

Guidelines for Investigators: Requirements for U.S. Army Medical Research and Materiel Command (USAMRMC) Headquarters Level Administrative Review and Approval of Research Involving Human Volunteers, Human Anatomical Substances, and/or Human Data

This document is divided into three sections.

Section 1 of the document provides definitions of terms used throughout the document (Part II), provides an overview of the requirements for USAMRMC Headquarters review, approval and oversight of research involving human volunteers, human anatomical substances and/or human data (Part III), and explains the review and approval process (Part IV).

Section 2 of the document provides suggested guidelines for writing protocols and consent forms that comply with Federal, DOD, Army, and USAMRMC requirements (Part V).

Section 3 provides information on where to go for help and information (Part VI) and contains Submission Checklists and Forms as well as other reference materials (Part VII).

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Section 1

I. Introduction

Research that is supported by the U.S. Army Medical Research and Materiel Command (USAMRMC) and involves human subjects, human anatomical substances, personally identifiable private information, or protected health information must be reviewed and approved by the USAMRMC Office of Research Protections (ORP) Human Research Protections Office (herein after referred to as the HRPO) prior to implementation.

The guidelines that follow highlight special requirements unique to DOD and USAMRMC supported research, detail the HRPO review and approval process, outline requirements for ongoing monitoring of research by the HRPO, and provide guidance on the elements that the HRPO requires in a protocol and consent form.

Specific guidelines are subject to change as governing regulations, policies, and procedures are updated.

II. Definitions

A. Research

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

B. Clinical Investigation

A clinical investigation is any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. This definition applies to research involving the use of FDA-regulated products. Even if a clinical investigation does not meet the definition of research, it is subject to the same regulations as research. Therefore, ***for the purpose of this document, clinical investigations will be considered research.***

C. Human Subject

A living individual about whom an investigator conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information. In this document, human subjects are also referred to as volunteers.

D. Human Anatomical Substances

Human anatomical substances include human organs, tissues, cells, or body fluids including but not limited to blood/sera (finger stick, ear stick, venipuncture, etc.), hair, nails, teeth, skin, sputum or cells gathered from mouth washing, nasal or oral swabs, placenta or amniotic fluid.

E. Individually Identifiable Private Information

Private information includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). *Individually identifiable* means that the identity of the subject is known or may readily be ascertained by the investigator or associated with the information.

F. Protected Health Information (PHI)

PHI is individually identifiable health information held by a covered entity, as defined in the Health Insurance Portability and Accountability Act (HIPAA).

G. Covered Entity

An organization engaged in treatment of patients, responsible for obtaining payment for such treatment, or engaged in other healthcare operations where PHI is electronically exchanged.

H. Authorization

Written permission from an individual allowing a covered entity to use or disclose specified PHI for a particular purpose (such as research).

I. Minimal Risk

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

J. Legally Authorized Representative (LAR)

An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

NOTE: State law defines who may act as a LAR. The Institutional Review Board (IRB) of record should be consulted for guidance regarding who can serve as a LAR for research at the research site.

K. USAMRMC Supported Research

For the purpose of this document USAMRMC supported research includes but is not limited to:

- Research conducted by the USAMRMC.
- Research supported (through facilities or personnel) by the USAMRMC.
- Research funded (through grant, contract, cooperative agreement, military interdepartmental purchase request, etc.) by the USAMRMC (e.g., Military Infectious Disease Research Program (MIDRP)).
- Research managed (technical management and/or funds management) by the USAMRMC as directed by Congress (e.g., Telemedicine and Advanced Technology Research Center (TATRC), Congressionally Directed Medical Research Program (CDMRP)).
- Research managed (technical management and/or funds management) by the USAMRMC on behalf of other Army or DOD organizations (e.g., Defense Advanced Research Projects Agency (DARPA)) through agreements.
- Research supporting Army Surgeon General Sponsored Investigational New Drug application or Investigational Device Application.
- Research managed by other DOD or Army organizations (e.g. Army Research Office (ARO), Chemical and Biological Medical Systems (CBMS)) who have agreements in place with the HRPO to provide the headquarters level review.

L. Intramural Research

Research conducted by USAMRMC Investigators or by USAMRMC organizations.

M. Extramural Research

Extramural research includes research that is supported by but not conducted by the USAMRMC.

N. Institutional Review Board (IRB) of Record

The IRB listed on an Institution's Assurance of Compliance (see section III. B.) that assumes responsibility for review and oversight of a research protocol on behalf of the

institution. An IRB of record from each institution engaged in the research must review and approve the protocol; therefore, there can be more than one IRB of record for a protocol. An IRB Authorization Agreement between two IRBs of Record allows one IRB of record to defer to another.

O. Research Proposal

Research plan submitted to the DOD funding agency in response to a solicitation. The proposal provides an overview of all proposed work to be performed and provides rationale as to why the institution should be awarded funds to complete the work. A proposal may consist of multiple research projects conducted under separate protocols at one or more institutions.

P. Research Protocol

A comprehensive, detailed and specific plan of action for execution of human subjects research. Refer to section V. of this document for the elements that should be included in a protocol.

Q. Award

Refers to a financial agreement such as a grant, contract, or cooperative agreement between the Federal Government and an institution

R. Scientific Review

Independent documented review that objectively evaluates the scientific merit of a research proposal or protocol. Refer to the HRPO Policies and Procedures document on the HRPO website for additional information on scientific reviews.

S. Contract Officer (CO)

Federal government employee authorized to negotiate awards and commit funds on behalf of the U.S. Government.

T. Contract Specialist

Federal government employee assigned to assist the CO with award related issues. The contract specialist is the primary point of contract for award related issues.

U. Contract Officer's Representative (COR)

Federal government employee assigned by the CO to manage the technical aspects and performance of an award on behalf of the DOD program office responsible for oversight of the research. The COR may serve as the **Grant Manager or Project Manager** or may have assistance from other personnel within the DOD program office

in executing COR responsibilities.

V. Human Subjects Protection Scientist (HSPS)

The HSPS is a federal government employee or contractor within the HRPO responsible for assisting investigators with the HRPO review and approval process. The HSPS is the investigator's primary point of contact for questions regarding the human research review process and other issues related to human subjects protection.

W. Army Human Research Protection Office (AHRPO)

The AHRPO is the office that reports to the Assistant Surgeon General, Force Projection and is responsible for human research policy, education, and oversight for the U S Army. The AHRPO administers DOD Assurances of Compliance.

X. Informed Consent.

Informed consent is an ongoing process that provides the subject, or legal representative (LAR), with sufficient details about a study so that he/she can make a voluntary decision about participation. Often a written consent form is employed to facilitate initial discussion of a study, and includes descriptions of study procedures, potential risks and benefits, and other pertinent information. Informed consent is an ongoing, interactive process and the subject's voluntary decision about continuing to take part in the trial should be reassessed throughout the study.

Y. Enrollment.

To register, enter, screen, randomize, or otherwise formally initiate a subject's participation in a study. Informed consent precedes enrollment. The number of subjects consented may differ from the number of subjects enrolled in a study (e.g. a subject may give consent to participate in a study but may be determined to be ineligible upon screening; commonly called a "screen failure"). NOTE: this definition may differ from that of a study sponsor.

Z. Screening.

A process of actively assessing a potential subject for inclusion in a study based on compatibility with pre-determined inclusion/exclusion criteria, ability and willingness to complete the study, and other factors. Screening that does not access, collect, or record a subject's protected health information may take place before informed consent is obtained. However, informed consent must be obtained prior to screening procedures that use protected health information or involve procedures that a subject would not normally undergo.

III. Overview of the Requirements for Approval of Human Research Supported by the USAMRMC

A. Regulatory Requirements

1. Federal Requirements

In 1991 the Department of Defense (DOD), together with 15 other federal agencies, adopted regulations that are known collectively as the Common Federal Rule. These regulations embody the ethical principles of the Belmont Report. Title 32 Code of Federal Regulations Part 219 (32 CFR 219), "Protection of Human Subjects," applies to all research involving human subjects conducted or supported by the DOD. The Department of Health and Human Services (DHHS) National Institutes of Health (NIH) corollary is 45 CFR 46. The DOD also adheres to the regulations found at 45 CFR 46 Subpart B (addresses research involving fetuses, pregnant women, and *in vitro* fertilization), Subpart C (addresses research involving prisoners), and Subpart D (addresses research involving children).

The USAMRMC also adheres to the Food and Drug Administration (FDA) regulation, 21 CFR (Parts 50, 56, 312, 812) for research involving investigational drugs or devices

The Health Insurance Portability and Accountability Act (HIPAA) of 1996 placed additional requirements on the use and disclosure of Protected Health Information (PHI) from covered entities. The USMRMC adheres to the Standards of Privacy of Individually Identifiable Health Information (the Privacy Rule) and the Standards for the Protection of Electronic Protected Health Information (the Security Rule) and the regulations set forth at 45 CFR 160-164.

2. DOD, Army, and USAMRMC Requirements

Research supported by the USAMRMC is also governed by DOD Directive (DODD) 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DOD Supported Research," 25 March 2002; Army Regulation (AR) 70-25, "Use of Volunteers as Subjects of Research," 25 January 1990, AR 40-7, "Use of Investigational Drugs and Devices and the Use of Schedule I Controlled Drug Substances," 19 October 2009. The OTSG maintains the overall responsibility for protecting human research volunteers for the Department of the Army.

DODD 3216.02 requires that DOD supported human subjects research must:

- Be conducted under an Assurance of Compliance for Protection of Human Research Subjects that is acceptable to the Army.
- Be reviewed and approved by a duly constituted IRB associated with the Institution's Assurance of Compliance or an IRB with which the institution has an authorization agreement.

- Receive a Headquarters (HQ) level review (second level review).

A HQ level or second level review is an additional requirement of the DOD that differs significantly from the NIH review process with which many awardees are familiar. Once a human research protocol supported by the DOD has been reviewed and approved or has been determined to be exempt by the IRB of record, it must undergo a HQ level or “second level” review that is coordinated by the human research oversight office of the DOD component (e.g., Army, Navy, Air Force, etc). Each DOD component has a unique process for accomplishing this required HQ level review.

The USAMRMC HQ ORP HRPO oversees the HQ second level review process for USAMRMC supported research. All USAMRMC supported research must be reviewed and approved by the HRPO *prior to implementation*. Certain research protocols may also be reviewed and approved by the Headquarters, USAMRMC Research Ethics Advisory Panel (REAP). The assigned HSPS will provide additional information for those projects that must be reviewed by the HQ USAMRMC REAP.

B. Assurance of Compliance for the Protection of Human Research Subjects

As required by 32 CFR 219.103, each institution engaged in USAMRMC-supported human subjects research must have an approved Assurance of Compliance for the Protection of Human Research Subjects in place prior to commencing research with human volunteers. Any awardee accepting funds that will support non-exempt human research is considered to be engaged in human research, even if the research is performed under a sub-contract or other financial agreement.

If an institution does not have a current Federalwide Assurance (FWA) with the DHHS Office for Human Research Protections (OHRP), an assurance must be obtained. The HSPS assigned by the USAMRMC ORP HRPO to review the project can provide assistance to investigators and engaged institutions that require a FWA or a DOD Assurance.

DHHS OHRP Federalwide Assurance (FWA). An OHRP FWA means that an institution has submitted all of the documentation OHRP requires to constitute a commitment by the institution to comply with the requirements set forth in 45 CFR 46 when its employees or agents engage in non-exempt human subjects research conducted or supported by HHS, or other research covered by the assurance.

Completion of an OHRP FWA Application. Information on how to obtain and submit a FWA application can be located at the following OHRP website:
http://www.hhs.gov/ohrp/assurances/assurances_index.html

DOD Assurance. All DOD institutions conducting human subjects research must have a DOD Assurance. A DOD assurance is a written commitment by the institution engaged in human research that the project will be conducted IAW the terms specified in the assurance document. DOD assurances must be negotiated by the USAHRPO and approved by the U.S. Army Assistant Surgeon General, Force Projection.

Completion of a DOD Application. To obtain a DOD assurance application from the AHRPO:

Director, U.S. Army Human Research Protections Office
2511 Jefferson Davis Highway
Room 11512
Arlington, VA 22202

703-601-4720 (voice)
703-601-3628 (facsimile)

For studies conducted outside of the United States, the international version of the assurance application should be completed.

C. Review by IRB of Record

The IRB of record for the engaged institution is responsible for review, approval and ongoing compliance oversight of the research. Documentation that the IRB of record reviewed and approved the protocol must be received prior to HRPO approval of the research.

If the research protocol is assessed as minimal risk (see section II for definitions), it can be approved by an IRB via expedited review if the study involves one of the research categories that qualify for expedited review, as listed in the Federal Register, Notices, Vol. 63, No. 216, dated November 9, 1998. A brief synopsis of these categories is located in Appendix I.

All human subjects research that is minimal risk but does not fall into one of the expedited review categories or that is greater than minimal risk must be reviewed at a convened IRB meeting with a majority of the members present.

The HRPO will review the submitted documentation to ensure concurrence with the exemption categories, waivers and expedited review procedures applied by the IRB of record. Any concerns regarding appropriate review will be discussed with the responsible individuals at the institution (usually the IRB office).

Although the HRPO provides second level review and oversight of the research, it relies on the IRB of record to closely monitor research studies, conduct the required continuing reviews, and to intervene as appropriate if significant issues arise.

D. Training for Research Personnel

Before conducting human subjects research, the investigators and key study personnel must complete human research protection training in accordance with their institution's requirements. Principal and Co-Investigators must submit documentation of the most recent human research protection training to the HRPO as part of the submission package for the protocol. Training may also be requested for other research personnel with significant interaction with research volunteers. The HRPO requires that human research protection training be successfully completed within the last three years. If research is to be conducted at an institution that does not have HSP education requirements established, contact the HRPO for guidance on appropriate training for the proposed research.

In addition, for all investigational drug and device protocols, successful completion of a course in the conduct of clinical research in accordance with Good Clinical Practices (GCP) is recommended for all investigators. GCP training is required for all investigators conducting protocols in support of an Army Surgeon General Investigational New Drug Application.

E. Compliance with the Health Insurance Privacy and Accountability Act (HIPAA) Privacy Rule

If research will be conducted within a covered entity or if protected health information will be retrieved from a covered entity, then compliance with the HIPAA Privacy Rule must be addressed. A HIPAA authorization for disclosure or documentation that the requirement for authorization has been waived by an IRB or Privacy Board must be provided. See Appendix J for HIPAA authorization waiver criteria. *Please note that HIPAA can apply to research that is exempt from the Common Federal Rule.*

F. DOD Unique Requirements

1. Title 10 United States Code 980 (10 USC 980)

When seeking DOD funding, investigators must consider Title 10 United States Code 980, which is applicable to DOD funded research. Title 10 United States Code 980 states that "Funds appropriated to the Department of Defense 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; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject."

Furthermore, and consistent with the Common Federal Policy for the Protection of Human Subjects, if an individual cannot give his or her own consent to participate in a research study, consent of the individual's legally authorized representative must be obtained prior to the individual's participation in the research. Moreover, 10 USC 980 prohibits enrollment of an individual not legally competent to consent (e.g.,

incapacitated individuals, incompetents, minors) in a DOD supported experiment unless the research is intended to benefit each volunteer enrolled in the study.

Recent DOD guidance on the applicability of 10 USC 980 limits the applicability to research involving an intervention or an interaction in which the primary purpose of the intervention or interaction is to obtain data on the effect of the intervention or interaction. Investigators planning on enrolling a population that does not have the capacity to provide informed consent should contact the HRPO for further guidance on the applicability of 10 USC 980.

10 USC 980 is applicable to most clinical trials. Investigators should be aware that this “intent to benefit” requirement often makes placebo controlled clinical trials enrolling incapacitated individuals, incompetents, or minors problematic. Investigators should, therefore, be able to articulate how this research intends to benefit these volunteers if they will be in the placebo arm of the trial. For example, a volunteer in the placebo arm may benefit directly from medical treatment or surveillance provided that is beyond the standard of care.

2. Medical Monitor

For research involving greater than minimal risk to volunteers, the DOD requires that an independent medical monitor must be appointed by name. Medical monitors can be physicians, dentists, psychologists, nurses, or other healthcare providers capable of overseeing the progress of research protocols, especially issues of individual volunteer/patient management and safety. Medical monitors must be independent of the investigative team and must possess sufficient educational and professional experience to serve as the volunteer/patient advocate. Depending on the nature of the study, the medical monitor may be asked to assess one or more of the following phases of a research project: volunteer recruitment, volunteer enrollment, data collection, or data storage and analysis.

At the discretion of the IRB or the HRPO, the medical monitor may be asked to discuss research progress with the principal investigator, interview volunteers, consult on individual cases, or evaluate adverse event reports for the safety and protection of the volunteers. Medical monitors shall promptly report discrepancies or problems to the IRB and the HRPO. They shall have the authority to stop a research study in progress, remove individual volunteers from a study, and take whatever steps are necessary to protect the safety and well-being of research volunteers until the IRB can assess the medical monitor’s report. At a minimum the HRPO requires that the medical monitor provide a written opinion regarding the relationship and outcome of any unanticipated problems related to participation, serious adverse events, and subject deaths.

The medical monitor should be identified in the protocol and their *curriculum vitae* and documentation of human subjects protection training must be provided with the protocol submission packet. The role of the medical monitor must be described in the protocol and be consistent with DOD guidance. It is acceptable to provide appropriate compensation to the medical monitor for his/her services.

3. Recruitment of Military Personnel

Civilian investigators attempting to access military volunteer pools are advised to seek collaboration with a military investigator who will be familiar with service specific requirements.

A letter of support from the Commander of military facilities or units in which the recruitment will occur or the study will be conducted will be requested by the HRPO. Some sites may also require that each volunteer seek written permission from their supervisor prior to participation in research studies. The Army, Navy (to include Marine populations), and Air Force all have specific requirements for human research. There may be additional service specific approvals required. Review by an IRB or other oversight office within the service may be required in addition to the IRB of record.

Special consideration must be given to the recruitment process for military personnel. The Chain of Command cannot be involved in the recruitment of military personnel and should not encourage or order soldiers to participate in a research study. Per DODD 3216.02, an ombudsman must be employed, for research posing greater than minimal risk, when conducting group briefings with Active Duty personnel to ensure that volunteers understand that participation is voluntary. An ombudsman may be considered for research posing no greater than minimal risk, and may be recommended in other situations as well, especially when young enlisted soldiers are recruited who are trained to follow orders. Soldiers are trained to act as a unit, so peer pressure should also be considered and minimized if possible.

4. Payment of Active Duty Military Personnel for Participation in Research

24 USC 30 limits payment to Active Duty military personnel for participation in research while on duty to blood donation and may not exceed \$50 per blood draw. Active duty research volunteers may not receive any other payment for participation in a research study unless they are off duty or on official military leave status at the time of their participation in the study.

5. Confidentiality for Military Personnel

Confidentiality risk assessment for military personnel requires serious consideration of the potential of a breach of confidentiality that may affect their military career. Measures to protect confidentiality should be carefully considered. Medical and psychological diagnoses can lead to limitation of duties or discharge. Information regarding alcohol or drug abuse, drunk driving, and sexual or spousal abuse could lead to actions under the Military Code of Justice including incarceration and dishonorable discharge. For aviators losing flight status due to a physical or psychological concern is an issue. Active duty personnel have a duty to report certain activities to the chain of command. Civilian study investigators are not bound by this requirement and may want

to consider obtaining a Certificate of Confidentiality that is intended to protect the researcher from being forced to disclose sensitive information.

G. Army and USAMRMC Requirements

1. Medical Care for Research-Related Injuries

The Common Rule requires that for greater than minimal risk research, volunteers be informed of the availability of medical treatment or compensation in the event of a research related injury and who will be responsible for covering the cost of any such injury.

In addition to the Common Rule requirements, the DoD D 3216.02 states that DOD organizations with primary involvement in the research are required to establish administrative procedures to protect human subjects from medical expenses (not otherwise provided or reimbursed) that are the direct result of participation in a research project involving more than minimal risk.

In consideration of the Common Rule and DODD 3216.02, the USAMRMC has provided further guidance for research that is funded through the USAMRMC, under USAMRMC Command Policy 2010-10. This policy defines USAMRMC primary involvement as research conducted in a USAMRMC facility or research being carried out by a USAMRMC Principal Investigator (PI).

For Research Conducted at USAMRMC Facility or by a USAMRMC Principal Investigator

(a) Subjects who are DOD healthcare beneficiaries are entitled to medical care for research-related injuries to the same extent that such medical care would be provided if the injuries were not research-related, as long as they remain healthcare beneficiaries. This care includes, but is not limited to free medical care at Army Medical Treatment Facilities (MTF).

(b) Subjects who are not DOD healthcare beneficiaries, or were but are not currently, are entitled to free medical care for research-related injuries at Army MTFs. However, it cannot be determined in advance which MTF will accept the subject.

(c) The USAMRMC does not provide compensation for research-related injuries, nor will the USAMRMC reimburse or pay medical expenses for the treatment of research-related injuries.

For USAMRMC Funded Research Conducted at a non-DOD facility or by a non-DOD PI

If USAMRMC-funded research is conducted in a non-DOD facility by a non-DOD PI, the DOD does not have primary involvement and the DODD requirement to protect subjects

from medical expenses for treatment of research-related injuries does not apply. Non-USAMRMC DOD facilities and non-DOD PIs are NOT covered by the new USAMRMC Command Policy but must comply with the DOD Directive. Therefore, prior to approval of a greater than minimal risk protocol that is conducted at a non-DOD facility or by a non-DOD PI there must be a plan in place to meet the requirement for non-DOD healthcare beneficiaries that may be enrolled.

For USAMRMC Funded Research Conducted at a DOD facility or by a DOD PI (non-USAMRMC)-

Non-USAMRMC DoD facilities/PIs are NOT covered by the new USAMRMC Command Policy but must comply with the DoD Directive. Therefore, prior to approving a greater than minimal risk protocol conducted at a DoD facility (or with a DoD PI), there must be a plan in place to meet the requirement for non-DoD healthcare beneficiaries that may be enrolled.

Study volunteers are authorized medical care in an Army Medical Treatment Facility for injury or disease that is a proximate result of their participation in Army supported research. If a research study could potentially result in a research related injury, the USAMRMC requires that, in addition to the medical care provisions of the institution performing the research, specific language be included in the consent form that describes the provisions for medical care available from the Army. Specific language to include can be found in section V.F.6. of this document.

2. U.S. Army Medical Research and Materiel Command Volunteer Registry Database

For certain research protocols the USAMRMC requires that investigators complete data sheets on all volunteers participating in the protocol for entry into the Command's Volunteer Registry Database. The Volunteer Registry Database contains items of personal information, such as names, addresses, social security number, and the name and dates of the respective study. This is a secure database with very limited access, and data sheets are destroyed after entry into the database. Information in the database will only be disclosed in accordance with Army Regulation 340-21 (the Army Privacy Program) and the Privacy Act of 1974. This means that only a person for whom data is collected or his/her designated agent, or legal guardian may request information from the database. Only authorized staff at the HRPO has access to information stored in the database.

The intent of the database is twofold: first, to readily answer questions concerning an individual's participation in research supported by the USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned of new risks and to provide new information as it becomes available. The information is stored at the USAMRMC for a minimum of 75 years.

Completion of data sheets for entry into the Volunteer Registry Database is **required for all greater than minimal risk intramural (see definition in section 1.2) studies and for all protocols supporting an Army Surgeon General sponsored investigational new drug (IND)**. At the discretion of the HRPO, greater than minimal risk extramural research may be required to comply with the Volunteer Registry Database requirement. If completion of data sheets is required, specific language to be included in the protocol and consent form can be found in section V (B and E) of this document. The Volunteer Registry Data Sheet (Form 60-R) can be found at Appendix G.

3. Research Involving the Use of Human Cadavers

Although research involving human cadavers is not considered to be human subjects research as defined by 32 CFR 219, the USAMRMC has a policy that requires HRPO review and approval of any research involving human cadavers if such research is designed to develop or test military protective gear and/or military equipment.

Consult the USAMRMC Command Policy “Ethical Use of Human Cadavers in USAMRMC Research” for guidance and further information on the documentation requirements for approval.

4. Disclosure of DOD Sponsorship and Access to Research Records

Volunteers must be informed early in the consent form that the DOD is supporting the research. Volunteers have a right to decline participation in research based on the source of the funding. In addition, representatives of the USAMRMC have the authority to review research records, which must also be disclosed to volunteers in the consent form.

5. Reporting Requirements to the HRPO

The HRPO requires approval of protocol amendments, acknowledgement or acceptance of continuing review documents, reporting of protocol deviations, serious adverse events, and unanticipated problems. The following is a synopsis of what must be reported (additional details on HRPO reporting requirements can be found in section IV.C.):

- Major amendments and amendments that increase risk to subjects must be pre-approved.
- All other amendments must be submitted for acceptance with the continuing review report.
- Unanticipated problems involving risks to subjects or others, serious adverse events related to participation, and deaths related to participation must be promptly reported.

- Suspensions, voluntary/involuntary clinical holds, or any terminations of the research must be promptly reported to the HRPO.
- Deviations that affect the safety or right of subjects or the integrity of the study must be promptly reported; exceptions (from approved inclusion/exclusion criteria or stopping criteria) must be pre-approved.
- Continuing Review reports and IRB approval documentation must be submitted as soon as the documentation is available. All amendments that occurred during the reporting period must be submitted at this time.
- The final study report and any supporting documents must be submitted to the HRPO as soon as all documents become available.
- The knowledge of any pending compliance inspection/visit by the FDA, OHRP, or other government agency concerning the DOD supported research, the issuance of Inspection Reports, FDA Form 483, warning letters, or actions taken by any Regulatory Agencies including legal or medical actions and any instances of serious or continuing noncompliance with the regulations or requirements must be reported immediately to the HRPO.
- Accurate and complete study records must be maintained and made available to representatives of the USAMRMC as a part of their responsibility to protect human subjects in research.

Note: On occasion, these reporting requirements, or elements of these reporting requirements, may be requested for inclusion in the body of the protocol.

IV. USAMRMC HRPO Process for Review, Approval, and Oversight of Research

A. Initial Review and Approval of Extramural Research

Proposals are submitted to the HRPO by the DOD program office managing the award (for example, CDMRP, TATRC, ARO). Proposals that entail one or more projects involving human subjects or human anatomical substances will require the development of a detailed research protocol for each project. The HRPO cannot begin review of a protocol until the proposal has first been received from the program. This generally occurs after a proposal is selected for funding but prior to finalization of the award. Once selected for funding, the DOD program office forwards the proposal to the HRPO where the protocol review and approval process may proceed during award negotiations.

Documentation of an independent review of the proposal for scientific merit is required and is provided to the HRPO by the DOD program office. This review is conducted during the proposal selection process and a copy is provided to the Principal Investigator by the program. While this review may raise human subjects protection

issues, it generally occurs prior to receipt of protocol documents by the HRPO and should not be mistaken for the HRPO review of the protocol. Investigators are encouraged to address weaknesses identified by scientific reviews, especially those that may mitigate risks to the volunteers. Any additional documentation that the Investigator has received to demonstrate that review of the protocol for scientific merit has occurred (e.g., minutes/approval from a scientific review committee or other body addressing science related issues) should also be provided.

When a proposal or protocol is received for review, the HRPO administrative staff initiates contact with the Investigator to verify contact information and to retrieve required protocol documents (See Exemption Submission Checklist at Appendix D and Protocol Submission Checklist at Appendix B for a complete list of documents and information required for HRPO review and approval).

If a research proposal is recommended for funding and the research involves human subjects, human anatomical substances, or privileged or protected health information, documentation must be submitted to the HRPO for review and approval prior to initiation of the USAMRMC supported research. Most human subjects research protocols are eligible to receive approval by the Deputy, ORP or designees (Chief, Human Subjects Protection Review) via HRPO administrative review. Certain research projects may require an additional review by the HQ USAMRMC REAP. The HSPS assigned to your project in preparation for HRPO review and approval will inform you and provide additional information if your research needs to be submitted to the HQ USAMRMC REAP.

1. Special Determinations

All USAMRMC proposals are triaged to determine whether there is a possibility that projects within the proposal require human subjects protection review and approval by the HRPO. In order for the HRPO to make a determination, additional information may be required.

In some cases a detailed protocol must be developed to gain enough information to make a determination. If existing human anatomical substances collected under other research protocols or by a tissue repository are being used, a blank copy of the consent form that was signed by volunteers when the anatomical substances were initially obtained for use in research may be requested. This documentation is necessary to assess whether at the time of original sample donation that the volunteers consented to the use of their samples in the type of research being conducted.

a. Determination that a Project does not Constitute “Research”

A USAMRMC supported proposal or project otherwise referred to as “research” may be determined by the HRPO not to meet the definition of research as defined by the Common Federal Rule (see section II. for definitions).

Determination notices are sent via e-mail to Investigators, CORs and Contract Specialists when the HRPO determines that a project does not meet the definition of

research. A determination may apply to part or all of the work to be conducted under the award. The work determined not to meet the definition of research will be specified in the determination notice.

b. Determination that Research does not Involve Human Subjects

A project can meet the definition of research, but not involve the use of human subjects, as defined by the Common Federal Rule (see section II. for definitions).

Determination notices are sent via e-mail to Investigators, CORs, and Contract Specialists when the HRPO determines that research does not involve human subjects. A determination may apply to part or all of the work to be conducted under the award. The research determined not to involve human subjects will be specified in the determination notice.

c. Determination that Human Subjects Research is Exempt from 32 CFR 219

Human subjects research may be exempt from the requirements of 32 CFR 219. A determination that a protocol qualifies for exemption must first be made by the appropriate office at the institution engaged in research (usually the IRB office). (Note that it is the policy of some institutions not to classify any human research as exempt from the Common Federal Rule). The HRPO usually does not issue an exemption determination if the IRB of record requires an expedited review. In this case the HRPO will follow the process for review of non-exempt research.

Investigators should consult their IRB for specific institutional requirements regarding review of research that might qualify for an exemption. Many institutions have developed specific forms and/or procedures for this purpose.

Once the exemption determination has been made by the Institution, a copy of the package of materials that were submitted for review (e.g., protocol, exemption/tissue use application, survey instruments, HRPO Claim of Exemption Form) with the accompanying determination letter should be submitted to the HRPO for review. An exempt determination memo from the HRPO must be issued prior to implementation of USAMRMC supported exempt human subjects research.

Because an Assurance of Compliance is only required for non-exempt research, the HRPO may waive the requirement to provide a determination from the IRB of record in cases where institutions do not have an assurance or an association with an IRB, such as small businesses. Waiver of this requirement will be considered on a case by case basis; however, if the HRPO determines the research does not meet the criteria for exemption, the institution must identify an IRB and pursue an Assurance of Compliance.

d. Review for Compliance with the Health Insurance Portability Accountability Act (HIPAA)

Projects involving the use of Protected Health Information (PHI) coming from within or provided by a covered entity are reviewed by the HRPO for compliance with applicable HIPAA regulations. To facilitate this process, Investigators should identify whether they are working at or obtaining PHI from a covered entity. Even if a project is determined not to meet the definition of research, not to be research involving human subjects, or to be exempt from 32 CFR 219, the use of Protected Health Information from Covered Entities must be reviewed by the HRPO to ensure compliance with applicable HIPAA requirements.

e. Waivers of Informed Consent or Documentation of Informed Consent, and HIPAA Authorization

A minimal risk protocol approved by expedited review can have the requirement to obtain informed consent waived by the IRB of record if it meets the criteria set forth in 32 CFR 219.116(d). See Appendix J. for these criteria. Documentation that the IRB of record approved the waiver must be submitted.

The HRPO will review the submitted documentation to ensure that a waiver of informed consent meets DOD/Federal regulatory requirements. Any concerns regarding appropriateness of the waiver will be discussed with the responsible individuals at the institution (usually the IRB office).

An IRB also has the authority to waive documentation of informed consent as outlined in 32 CFR 219.117. See Appendix J. for these criteria. Documentation that the IRB of record approved the waiver must be submitted.

The consent process must still occur, but the requirement to obtain a signed consent form is waived. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide volunteers with a written statement regarding the research.

The HRPO will review submitted documentation to ensure that a waiver of documentation of consent meets DOD/Federal regulatory requirements. Any concerns regarding the appropriateness of the waiver will be discussed with the responsible individuals at the institution (usually the IRB office).

The IRB of record or Privacy Board for a covered entity has the authority to waive the requirement to obtain a of HIPAA authorization for use or disclosure of protected health information as outlined in 45 CFR 164. See Appendix J. for these criteria. Documentation that the IRB of record or Privacy Board approved the waiver must be submitted.

The HRPO will review the submitted documentation to ensure that a waiver of HIPAA authorization meets Federal requirements. Any concerns regarding appropriateness of

the waiver will be discussed with the responsible individuals at the institution (usually the IRB or Privacy office).

2. HRPO Review and Approval of Non-Exempt Research

All non-exempt human subjects research protocols are assigned to a HRPO HSPS once required protocol documents have been received. The HSPS:

- provides guidance to investigators on the review process to include requirements unique to the DOD, the Army, and the USAMRMC.
- conducts a detailed human subjects protection review of the protocol and supporting documents (see Protocol Submission Checklist at Appendix B).
- assists the investigator with obtaining the required HRPO approvals.
- follows the project throughout the period of performance.
- serves as the investigator's primary point of contact for questions or issues regarding the human subjects protection review.

After submission of a complete protocol packet, the HSPS provides initial feedback from the HRPO to the Principal Investigator (PI). Revisions to protocol and consent form documents may be required to meet standards for approval by the HRPO. Close adherence to the guidance provided in this document will minimize the need for such revisions to submitted documents. Once all HRPO concerns have been adequately addressed, an approval memorandum is distributed via e-mail.

3. HQ USAMRMC Research Ethics Advisory Panel (REAP) Review

The HQ USAMRMC REAP consists of a standing panel of experts who have specialized training relevant to the scientific and ethical issues present in USAMRMC supported research. From this panel, HRPO identifies members with relevant expertise to form subcommittees which provide HRPO with independent subject matter expert review and advice for selected studies and/or issues that present unique regulatory and ethical challenges.

b. The HQ USAMRMC REAP subcommittees will review human subjects research involving the following:

- (1) Gene transfer technologies;
- (2) Requests for Secretary of the Army waiver of the 10 USC 980 requirement for advanced informed consent;
- (3) Complex ethical, risk/benefit, and/or other safety, rights, or welfare issues as identified by the Director, HRPO;

(4) Non-compliance cases as determined necessary by the Director, HRPO;

(5) Human Subjects research studies that HRPO approval authorities recommend disapproving;

(6) Research or research-related issues as determined necessary by Director, HRPO.

For studies requiring review by the HQ USAMRMC REAP, the assigned HSPS will inform the Investigators of this requirement and assist them with preparing documentation for review. During the review, the assigned HSPS or HRPO staff may request additional information and documents from the Principal Investigator to facilitate the review by HQ USAMRMC REAP Subcommittee members.

HQ USAMRMC REAP Subcommittee members provide non-binding recommendations to the CG, USAMRMC and HRPO. HRPO will review the recommendations and develop a course of action, including the requirements for HRPO approval. The HSPS will provide the requirements and stipulations from the HQ USAMRMC REAP review to the Principal Investigator (PI). Additional revisions to protocol and consent form documents may be required to meet standards for approval by the HRPO. Once the Director, HRPO (or designee) determines that the research meets the HRPO requirements, HRPO will provide written approval to the Principal Investigator.

4. Review and Approval of Multi-site Protocols

For multi-site protocols the HRPO must review and approve implementation of the protocol at each research site supported by the USAMRMC. The “master protocol” or protocol and consent form for the primary site are first reviewed and approved by the HRPO as appropriate. For each subsequent site a site-specific protocol or a master protocol with a site specific addendum describing the site-specific implementation of the protocol at each site (e.g., roles and responsibilities of personnel, recruitment and consent process, site specific reporting requirements, etc.), consent form, and other site specific documentation must also receive HRPO review and approval after review and approval of the protocol and consent form for the primary site. See Appendix C for site submission requirements for multi-site protocols. In addition, as described in section III.B above, all domestic and foreign sites are required to assure compliance with the federal policy for the protection of human subjects.

B. HRPO Initial Review and Approval of Intramural Research

Research conducted at USAMRMC laboratories or facilities or by USAMRMC personnel is considered intramural to the USAMRMC. The review process for intramural research follows the process outlined above with the following major exceptions:

- Research determined to be no greater than minimal risk by the IRB at the USAMRMC laboratory can be approved for implementation by the Commander after review and approval by the IRB. The HRPO provides oversight for these studies via

periodic review during site visits to the laboratories.

- In most cases the IRB office at the laboratory will handle transmission of documents to the HRPO for review and approval as required. USAMRMC Investigators should check with the IRB office for institute-specific procedures for submission. USAMRMC Investigators engaged in human subjects research who are not assigned to a USAMRMC laboratory with an IRB should contact the HRPO for further assistance with the review process.

C. HRPO Oversight of Ongoing Research

1. Protocol Modifications and Amendments

After the protocol is approved by the HRPO, any modifications (amendments) to the protocol, consent form, advertisements, questionnaires, or other related study documentation must be submitted to the local IRB for approval prior to implementation.

Major modifications to the research protocol and any modifications that could potentially increase risk to volunteers must be submitted to the HRPO for approval prior to implementation. All other amendments must be submitted with the continuing review report to the HRPO for acceptance. Some examples of major modifications include a change in Principal Investigator (PI), change or addition of an institution, elimination or alteration of the consent process, change in age range, or change in/addition to the study population, and changes that could potentially increase risk to subjects.

For amendments that require approval by the HRPO, prior to implementation, the PI must submit:

- A description of proposed modifications or amendments to the protocol and an explanation of the need for these modifications should be submitted
- Any revised protocol documents incorporating the modifications. If the IRB of record did not require revision of protocol documents, submit a copy of all documentation submitted to the local IRB for approval of the modifications.
- Documentation of IRB approval of the changes.
- Note that for major study design changes additional scientific review may be required.
- For FDA regulated studies a statement from the FDA accepting the amendment may also be requested.

NOTE: Although the HSPS works closely with the COR at the program office and the CO at the contracting office, neither the HSPS nor the HRPO have the authority to approve changes in statements of work (SOW), changes in awardee Institution,

changes in PI, or to commit government funds. If an amendment to a protocol affects the SOW, a revised SOW must be submitted to the DOD program office. The program office must recommend approval to the CO and a modification to the award must be made.

A change in SOW, a change in PI, or a change in Institution may also require review and approval by the HRPO because it adds or changes a project, site, or invokes an amendment. Coordination with the COR and CO should occur PRIOR to submission of the amendment to the local IRB or the HRPO for review, in case the request is disapproved.

Submitted documentation will be reviewed by the assigned HSPS and additional information or revisions may be requested. Once all outstanding issues are addressed, the HRPO will issue an approval memorandum for the amendment.

Minor amendments that do not increase risk to volunteers do not require review and approval by the HRPO prior to implementation; however, documentation related to the amendment (the same documents listed above) must be submitted along with the continuing review report for acceptance by the HRPO.

2. Reporting of Unanticipated Problems and Serious Adverse Events (SAEs)

The following must be promptly reported to the HRPO:

- Unanticipated problems involving risk to volunteers or others.
- Serious adverse events related to participation in the study.
- Volunteer deaths related to participation in the study.

Reports may be forwarded to the HQ USAMRMC REAP for additional review at the discretion of the HRPO.

Elements to include in the report are also provided in Appendix K. The USAMRMC policy for Reporting of Unanticipated Problems on the HRPO website provides a sample reporting form that includes all of the elements required to be reported. Investigators may use this form if there is no equivalent available at their local institution. If the institutional form or study specific form does not contain all of the elements the HRPO requires in order to evaluate the event, additional information may be requested from the Investigator by the HRPO staff. For adverse drug experiences submission of a Medwatch form is acceptable. The unanticipated problems and/or SAE should be promptly reported by phone (301-619-2165), by email (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the HRPO.

A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the USAMRMC, ATTN: MCMR-RPH, 504 Scott Street, Fort Detrick, Maryland, 21702-5012.

Unanticipated problems resulting in risk to volunteers or others encompass more than what one usually thinks of as adverse events. “Problems involving risk” may not necessarily result in harm. For example, misplacing a volunteer’s study records containing identifiable private information introduces the risk of breach of confidentiality. Confidentiality may or may not be breached, but either way this would be a reportable event. Another example would be administering the wrong agent to a volunteer at one time point in a series of vaccinations. Risks to others must also be reported. For example, an unexpected outburst by a volunteer that puts other volunteers and/or study staff at risk would be a reportable event.

For studies with a medical monitor assigned, the Investigator must inform the medical monitor of any unanticipated problems or SAEs. See section V.B.20 for details regarding the medical monitor’s role in reviewing adverse events. Follow-up reports should be submitted until resolution of the unanticipated problem. Appropriate supporting documents, such as laboratory reports, pathology reports, and discharge summaries should be submitted with the unanticipated problem or serious adverse event report. Documentation of any action taken by the IRB of record in response to the event should be provided when available.

The HRPO will evaluate reported information to determine if changes are warranted in the research protocol or protocol-related documents or in the information provided to volunteers. Any changes required by the local IRB should be communicated immediately to the HRPO. Once any safety issues are appropriately addressed, an acceptance memorandum will be issued for all reportable events. Events that are reported that do not meet the HRPO reporting criteria (such as adverse events with no relationship to the study) will be placed in the HRPO protocol file; however, HRPO does not routinely issue acceptance memorandums for these events.

3. Reporting Protocol Deviations

Any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study must be promptly reported to the HRPO. Any corrective actions taken to avoid future deviations should be included in the report. Documentation of any actions taken by the IRB of record related to the deviation report should be provided when available.

The HRPO will review the deviation report along with any actions taken by the IRB and either request further information/clarifications, request additional corrective actions, or accept the deviation report. An acceptance memorandum will be issued for deviations that meet the HRPO reporting criteria. Deviations that are reported that do not meet the HRPO reporting criteria will be placed in the HRPO protocol file; however, the HRPO does not routinely issue acceptance memorandums for these deviations.

4. Continuing Review and Final Reports

All continuing review reports and the final report approved by the local IRB must be

submitted to the HRPO. A continuing review of the protocol must be completed by the local IRB at least once each year for the duration of the study. Items that should be included in the continuing review report can be found in Appendix F.

A copy of the approved continuing review report and the local IRB approval notification must be submitted to the HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification must be submitted to the HRPO as soon as these documents become available.

The HRPO Continuing Review Analyst (CRA) assists the assigned HSPS with review of continuing review and final report documentation. The CRA sends a reminder to the Principal Investigator 60 days in advance of the continuing review due date on file at the HRPO. Additional reminders will follow if documentation of re-approval is not received by the study expiration date on file with the HRPO. Documentation related to any amendments that did not require review by the HRPO prior to implementation should be submitted along with the continuing review documentation for acceptance.

Please note that the continuing review report and final report are not the same as the annual technical report and final report that is submitted to the DOD program office addressing the progress/outcome of the grant. The documents submitted to the IRB of record for re-approval of the protocol are the documents that should be submitted for continuing review. The documents submitted to the IRB of record to request closure of the protocol are the documents required as the final report.

The CRA performs an initial review of the submitted documents and may request additional information/clarifications. The HSPS assigned to the protocol will review any actions that have occurred since the initial approval or last continuing review (e.g. amendments, SAEs, deviations) and address any concerns with the Investigator. Concerns regarding accrual are referred to the DOD program office managing the award.

Serious concerns will be referred to the Commanding General, USAMRMC and actions recommended could include rescinding the HRPO approval of the research. **Please note that although the HRPO can take action to rescind its approval of a protocol upon review of the continuing review documentation, re-approval by the HRPO is not required in order for a study to continue, as it is with the IRB of record.**

The HRPO will issue an acceptance memorandum once all documentation has been received; reviewed and any outstanding issues have been resolved.

5. Routine and For Cause Site Visits

The HRPO conducts routine and for cause study site visits to monitor ongoing research supported by the USAMRMC. Site visits might be directed by the HRPO as a condition of initial approval, may be random, or may be conducted to investigate a specific issue or concern raised by submitted documentation or other means. Refer to the HRPO Policies and Procedures available on the HRPO website for additional information

regarding site visits.

Section 2

V. Guidelines for Writing Research Protocols Involving Human Volunteers

The USAMRMC does not require a specific protocol format; however, specific topics must be addressed within the protocol/protocol documents as described below. In addition, the Protocol or Exempt Protocol Submission Checklist should be completed, signed, and dated by the PI and submitted with the protocol submission to the HRPO.

A. Protocol Format

A detailed research protocol must be submitted for each research study involving human subjects or human anatomical substances (See Appendix B for the complete list of documents required for HRPO review). The HRPO accepts the protocol/protocol application format that is required by the IRB of record; however, if this format does not include all of the information that the HRPO requires to evaluate the protocol, additional information and/or revisions will be required.

All documents that will be submitted for review by the IRB of record (to include IRB applications) must be forwarded for to HRPO for review. To streamline the review process, the HRPO will on occasion, review protocols and provide input prior to review by the IRB of record, but IRB of record approval must be in place before a protocol receives final HRPO approval.

Although the HRPO does not insist on use of a standard protocol template, all elements described below that are applicable to the research being conducted should be addressed within the protocol that is submitted to the IRB of record for approval.

Both IND and Investigational Device Exemption (IDE) protocols should follow the format and include the elements described in the International Conference on Harmonisation (ICH), Consolidated Guideline E6 (<http://www.ich.org/cache/compo/475-272-1.html#E6>).

B. Required Elements of the Protocol

1. Protocol Title.

2. PI/Study Staff. List the complete name, address, telephone and fax number, and e-mail address of the PI. Include a copy of the PI's *curriculum vitae* (CV) or biosketch with the protocol. List the names of all key study personnel who will have significant involvement in the research study; include their professional credential (i.e., MD or RN), highest degree(s), job title, and employing institution and provide CVs or biosketches.

3. Study Location(s). List all centers, clinics, or laboratories where the study is to be conducted. Provide the Federalwide or DOD Assurance number for each institution engaged in research. Include the name, degree(s), title, employing institution, and complete address of the investigator(s) for each research site.

4. Background. Include a literature review that describes in detail the rationale for conduct of the study. Include descriptions of any preliminary studies and findings that led to the development of the protocol. The background section should clearly support the choice of study variables and explain the basis for the research questions and/or study hypotheses. This section establishes the relevance of the study and explains the applicability of its findings.

Note: If the protocol was initiated using other funding prior to obtaining the DOD funding, explain the history and evolution of the protocol and declare the source of prior funding. Specifically identify the portions of the research that will be supported with DOD funds. For ongoing protocols the HRPO approval is required prior to initiation of any human subjects research activities supported by USAMRMC.

5. Objectives/Specific Aims/Research Questions. Provide a description of the purpose and objectives of the study with detailed specific aims and/or research questions/hypotheses.

6. Research Design. Describe the type of study to be performed (e.g., prospective, retrospective, randomized, controlled, etc.) and outline the proposed methodology in sufficient detail to show a clear course of action.

- Define the study variables and describe how they will be operationally measured.
- Describe the methods that will be used to obtain a sample of volunteers from the accessible population (i.e., convenience, simple random, stratified random).
- If applicable, describe the subject to group assignment process (e.g., randomization, block randomization, stratified randomization, age-matched controls, alternating group, or other procedures).
- Explain the specific actions to accomplish the group assignment (e.g., computer assignment, use of table of random numbers).
- Describe the reliability and validity of psychometric measures.

7. Study Population. Describe the target population (to whom the study findings will be generalized) and the nature, approximate number and pertinent demographic characteristics of the accessible population at the study site (population from which the sample will be recruited/drawn). Volunteer selection should be equitable. The protocol should include justification of any age, race, ethnicity, or sex limitations provided.

8. Inclusion/Exclusion Criteria. List the inclusion and exclusion criteria in the protocol. Inclusion/exclusion criteria should take into consideration the specific risk profile of the study to be conducted. Ensure that exclusions are justified. Diseases, medications, and groups of volunteers that should be excluded should be clearly stated.

Inclusion of Women and Minorities in Research. Consistent with the Belmont Report and recent congressional legislation, special attention is given to inclusion of women and minorities in research funded or supported by the USAMRMC. This policy is intended to promote equity both in assuming the burdens and in receiving the benefits of human subjects research. If women and/or minorities will be excluded from the protocol, an appropriate justification must be included.

9. Description of the Recruitment Process. Explain methods for identification of potential study participants (e.g., medical record review, obtaining sampling lists, health care provider identification, etc.)

Describe the recruitment process in detail. Address who will identify potential volunteers, who will recruit them, and what methods will be used to recruit them.

If volunteers will be compensated for participation in the research study, a detailed description of the compensation plan should be included in the protocol. Ensure that the compensation plan is fair and does not provide undue inducement. If the study requires multiple visits, a plan for pro-rating payments in the event of volunteer withdrawal should be considered.

Provide copies of all recruitment and advertisement materials for review as part of the submission. The recruitment materials should not be coercive or offer undue inducements and should accurately reflect the research. An ombudsman should be considered for use with particularly vulnerable populations. See section III.F.3 above for additional information specific to recruitment of military personnel and section V.D below for additional guidance on recruitment materials.

10. Description of the Informed Consent Process. Specifically describe the plan for obtaining informed consent from study volunteers.

- Identify who is responsible for explaining the study, answering questions and obtaining informed consent.
- Include information regarding the timing and location of the consent process.
- If applicable, address issues relevant to the mental capacity of the potential volunteer (e.g., altered capacity due to administration of any mind-altering substances such as tranquilizers, conscious sedation, or anesthesia, brain injury, stress life situations, or volunteer age).

- Address how privacy and time for decision-making will be provided and whether or not the potential volunteer will be allowed to discuss the study with anyone before making a decision.
- As consent is an ongoing process, consider the need for obtaining ongoing consent or for re-assessing capacity over the course of a long term study and describe any relevant procedures to assure continued consent.
- If volunteers will be included in the study who cannot give their own consent to participate, there must be a plan for the consent of the individual's LAR to be obtained prior to the volunteer's participation in the study. State law defines who may act as an LAR. The IRB of record should be consulted for guidance regarding who can serve as an LAR for research at the research site.
- If illiterate volunteers are anticipated, the consent process to be followed for illiterate volunteers should be outlined in the protocol. The consent form should be verbally read/explained to the volunteer in the presence of a witness. The volunteers must sign or make a mark (such as a thumbprint) to indicate agreement to participate and the witness must sign to attest that the content of the written consent form was accurately conveyed to the volunteer.
- If it is anticipated that volunteers who do not speak the primary language of the host country will be enrolled into a trial, all documentation provided to volunteers (consent form, information sheets, etc.) should be translated with a copy provided to the HRPO for review. A plan for ensuring that volunteers questions can be addressed during the consent process and throughout the trial should be included.
- If a waiver of all or parts of the consent process is being sought or a waiver of documentation of consent is desired, justification of why the waiver should be considered to include how the protocol meets the criteria set forth in 32 CFR 219 should be included in the protocol. These criteria can be found in Appendix J. If consent to use existing samples or data in future research was provided as a part of another research protocol, this should be clearly explained. If the institution is a covered entity, justification for HIPAA authorization waiver requests should also be provided.

NOTE: When consent will be obtained in a language other than English, documentation that the foreign language version of the consent form is an accurate translation of the English version of the consent form must be provided to the HRPO. Documentation from a qualified translator certifying the translation must be provided along with the English and foreign language version of the consent forms. The documentation of translation should include a statement certifying that the translation is accurate and true, as well as the signature, name, address, phone number, and, if available, fax number of the translator.

Assent - When minors are included in research, a plan to obtain assent (agreement) from those with capacity to provide it or a justification for a waiver of assent should be provided. The HRPO, on occasion may require that age appropriate assent forms be developed for use with minors when assent is obtained. Capacity to provide assent should also be considered for other populations that cannot provide informed consent and assent should be obtained whenever possible.

11. Volunteer Screening Procedures. List and describe any evaluations (e.g., laboratory procedures, history, or physical examination) that are required to determine eligibility/suitability for study participation and the diagnostic criteria for entry. Please note that some screening procedures may require a separate consent or a two-stage consent process. Informed consent must be obtained prior to initiation of any procedures for collection of individually identifiable private information for the purposes of determining eligibility.

12. Study Procedures/Research Interventions. Describe the research intervention or activity that the volunteer will experience. Provide sufficient detail in chronological order for a person uninvolved in the research to understand what the volunteer will experience and when it will occur. Provide a schedule of study evaluations and follow-up procedures. Provide all case report forms, data collection forms, questionnaires, rating scales, and interview guides, etc. that will be used in the study.

13. Description of Protocol Drugs or Devices. If the protocol uses a drug, biologic, device, or dietary supplement, provide the following information:

- For medical products regulated by the Food, Drug, and Cosmetic Act, designate the protocol as Phase I, II, III, or IV research.
- If the study is in support of an application to the FDA, provide the IND/IDE number and name of the sponsor.
- Provide complete names and composition of all medication(s), device(s), or placebo(s).
- Identify the source of medications, devices, or placebos.
- Describe the location of storage for study medications.
- Describe the dose range, schedule, and administration route of test articles.
- Describe washout period, if used, in detail.
- Describe the duration of drug or device treatment.
- Declare concomitant medications allowed.

- Identify any antidotes and treatments available for potential side effects.
- Describe the plan for disposition of unused medication/devices.
- For FDA regulated studies, describe the procedure by which the IND sponsor will monitor the protocol in accordance with 21 CFR 312.

14. Laboratory Evaluations.

- Specimens to be collected, schedule, and amount. All specimens that will be collected for research purposes must be clearly stated in the protocol. The collection schedule and amount of material collected must also be clearly described. This may be represented using a table or schematic for more involved protocols.
- Evaluations to be made. All evaluations that will be made for research purposes should be stated in the protocol. Copies of all data collection forms must be provided. The protocol should explain how the results of laboratory evaluations will be used to meet the objectives of the research (or to monitor the safety of volunteers).
- Storage. Specimen storage must be described in the protocol to include where, how long, any special conditions required, labeling, and disposition. If there is a plan to store specimens for future use (either by the Investigator or through an established repository), this should be outlined in the protocol. If samples will be collected for future use in other research (and if this is not the sole purpose of the protocol), volunteers should be given the chance to opt out. Potential future uses of samples should be addressed to the degree possible. If volunteers are given a menu of options regarding sample donation for future research, procedures should be in place to ensure that volunteers' wishes for use of samples are honored. Procedures for withdrawal of samples at the request of the volunteer should be described if samples will remain coded or identified.
- Labs performing evaluations and special precautions. The laboratory performing each evaluation should be clearly identified in the protocol, as well as any special precautions that should be taken in handling the samples. Special precautions that should be taken by the volunteer before, during, or after the laboratory procedure should be clearly defined. If transport of samples is required, provisions for ensuring proper storage during transport should be included in the protocol.

15. Sample Size Justification. An appropriate sample size justification (for example, power analysis) must be included in the protocol to ensure that the sample size is appropriate to meet the objectives of the study. The protocol should specify the approximate number of volunteers that will be enrolled. If the protocol involves multiple sites, the number enrolled at each site should be stated in the master protocol.

16. Data Analysis. Describe the data analysis plan. The data analysis plan should be consistent with the study objectives.

17. Data Management.

- Methods Used for Data Collection. All methods used for data collection should be described in the protocol. Copies of data collection forms and any test instruments administered should be provided. Data collection forms should be adequate and accurate according to the data collection plan described in the protocol. Whenever possible, identifiers should be removed from data collection forms. Critical measurements used as endpoints should be identified.
- Volunteer Identification. If unique identifiers or a specific code system will be used to identify volunteers, this process should be described in the protocol.
- Confidentiality.
 - The protocol should explain measures taken to protect the privacy of research volunteers and maintain confidentiality of study data. Strategies to protect the privacy and confidentiality of study records, particularly those containing identifying information, should be addressed. Investigators collecting particularly sensitive information should consider obtaining a Certificate of Confidentiality.
 - The protocol should address who will have access to research records, data, and specimens. The protocol should acknowledge that representatives of the USAMRMC are eligible to review research records.
 - Requirements for reporting sensitive information to state or local authorities should be addressed in the protocol. Examples of sensitive information that may require reporting include positive human immunodeficiency virus (HIV), hepatitis, or tuberculosis test results, illegal residency, child or spouse abuse, or participation in other illegal activities. These requirements will vary from state to state. Investigators should consult their IRB for assistance with state requirements.
- Disposition of Data. Describe where data (both electronic and hard copy) will be stored, who will keep the data, how the data will be stored, and the length of time data will be stored. Note that records of IND studies must be kept until 2 years after a New Drug Application is approved/issued or for 2 years after the IND is withdrawn. Records required for IDE studies should be retained for 2 years following the date that the investigation is terminated or completed or the date that the records are no longer required for support of the pre-market approval application, whichever is sooner.

- Sharing Research Results. In cases where the volunteer could possibly benefit medically or otherwise from the information obtained during the research, the protocol should explain whether or not the results of screening and/or research participation will be shared with volunteers or their primary care provider, to include results from any screening or diagnostic tests performed as part of the research. The potential benefits of providing volunteers with the information should be weighed against the potential risks. It is generally not advisable to use experimental assays or techniques to guide clinical care.

18. Risks/Benefits Assessment.

- Foreseeable Risks. The protocol should clearly identify all research risks. Research risks include any risks that the volunteer is subjected to as a result of participation in the protocol. Consider psychological, legal, social, and economic risks as well as physical risks. If the risks are unknown, this should be stated in the protocol. If applicable, any potential risk to the study personnel should be identified.
- Risk Management and Emergency Response.
 - Describe measures to be taken to minimize and/or eliminate risks to volunteers and study personnel or to manage unpreventable risks. All safety measures in place to mitigate risk (e.g., core temperature monitoring, electrocardiogram (ECG) monitoring, observation periods, special procedures to avoid disclosure of potentially damaging information) should be described.
 - Describe planned responses such as dose reduction or stopping criteria based on toxicity grading scales or other pre-determined alert values and other safeguards should be detailed in the protocol.
 - If there is a chance a volunteer may require emergency care or treatment for an adverse event, the protocol should discuss the overall plan for provision of care for research related injuries to include who will be responsible for the cost of such care. For example, if a study sponsor or institution has committed to providing care for research related injury at no cost to volunteers, this provision should be explained in the protocol. Refer to section III.G.1 for information regarding the provision of medical care for research conducted at USAMRMC facilities or by a USAMRMC principal investigator. The clinical site must have adequate personnel and equipment to respond to expected adverse events, and the nearest medical treatment facility should be identified in the emergency response plan.
 - Describe any special precautions to be taken by the volunteers before, during, and after the study (e.g., medication washout periods, dietary restrictions, hydration, fasting, pregnancy prevention, etc.) must be addressed. If pregnant volunteers will be excluded from participation in the

study, the method used to determine pregnancy status in women of childbearing potential must be specified. Also, state the time that will elapse between the pregnancy test and exposure to research procedures or medical products and how long the non-pregnant volunteer should use effective contraceptive practices after participating in the study. Please note that contraceptive practices may be necessary for male volunteers participating in certain types of studies. For IND studies pregnancy testing is recommended within 48-72 hours before the start of the study. Consideration should be given to repeating testing prior to administration of test articles.

- Describe any special care (e.g., wound dressing assistance, transportation due to side effects of research intervention impairing ability to drive) or equipment (e.g., thermometers, telemedicine equipment) needed for volunteers enrolled in the study must be described in the protocol.
- Potential Benefits. Describe real and potential benefits of the research to the volunteer, a specific community, or society. Ensure that the benefits are not overstated.

NOTE: Payment and/or other compensation for participation are not considered to be benefits and must be addressed in a separate section.

- Intent to Benefit. If volunteers cannot give their own consent to participate in an experimental study, and 10 USC 980 applies, a clear intent to benefit each volunteer must be described in the protocol. Refer to section III.F.1 of this document for additional information regarding 10 USC 980.

19. Study Personnel.

- Roles and Responsibilities of Key Study Personnel. Briefly describe the duties of key study personnel. Describe their roles in the research effort (e.g., Jane Doe, MSN, Research Coordinator: recruit and consent volunteers, maintain study records, administer study drug, take and record vital signs, enter data into computer data base).
- Conflict of Interest. Investigators and key study staff must disclose any real or apparent conflicts of interest (financial or other). This information may be provided in the protocol or by submission of a conflict of interest declaration form. (Many institutions have a form for this purpose, as does the FDA. A Financial Disclosure Form for Investigators is also available on the HRPO website that will meet this requirement). Measures taken to mitigate the impact of conflicts of interest must be provided. Information regarding conflicts of interest should be disclosed to volunteers in the consent form. All protocols that support development of a drug, device, or other intellectual property require completion of a conflict of interest declaration by all investigators on the protocol. Other protocols may require conflict of interest statements on a case-by-case basis.

20. Medical Monitor

- Roles and Responsibilities of Medical Monitor. The DOD requires that a medical monitor be assigned to greater than minimal risk protocols. The specific roles the medical monitor will fulfill should be outlined in the protocol, and the medical monitors name should appear in the protocol. See section III.F.2 for additional information regarding the medical monitor requirement.

Note: The HRPO requires that the medical monitor review all unanticipated problems involving risk to volunteers or others, serious adverse events, and all volunteer deaths associated with the protocol and provide an unbiased written report of the event within ten calendar days. At a minimum the medical monitor should comment on the outcomes of the adverse event and relationship of the event to the protocol or test article. The medical monitor should also indicate whether he/she concurs with the details of the report provided by the PI. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the HRPO.

21. Withdrawal from the Protocol. Volunteers may discontinue participation in the research at any time without penalty or loss of benefits to which the volunteer is otherwise entitled. If appropriate, the protocol should describe the procedure in place to support an orderly end of the volunteer's participation (e.g., exit exam or follow-up safety visits outside of the context of the research study, information regarding prorated payment for partial participation, etc.) and the consequences of a volunteer's decision to withdraw from the study. The anticipated circumstances under which the volunteer's participation may be terminated by the investigator or others should also be addressed (e.g., non-compliance, safety issues, loss of funding, etc.).

22. Modifications to the Protocol. Describe the procedures to be followed if the protocol is to be modified, amended, or terminated before completion. Note that any modification to the protocol, consent form, and/or questionnaires, including a change to the PI, must be submitted to the local IRB for review and approval. Major modifications to the research protocol and any modifications that could increase risk to volunteers must be submitted to the HRPO for approval prior to implementation. Some examples of major modifications include a change in PI, change or addition of an institution, elimination or alteration of the consent process, change in subject age range, or change in/addition to the study population, and changes that could potentially increase risk to subjects. All other amendments will be submitted with the continuing review report to the HRPO for acceptance. Address the procedures for submitting amendments even if modifications to the protocol are not anticipated.

23. Protocol Deviations. Describe procedures and notifications to be made in the event of deviations from the approved protocol to include both the local IRB and the HRPO.

Note: Any deviation to the protocol that may have an effect on the safety or rights of the volunteer or the integrity of the study must be promptly reported to the HRPO.

24. Reporting of Serious Adverse Events and Unanticipated Problems.

- Reporting procedures will differ from institution to institution, so it is important for investigators to identify the reporting requirements for all entities involved in review of the protocol and to clearly define this procedure within the protocol.
- Serious adverse events and unanticipated problems can occur in any and all types of studies, not just experimental interventions or clinical trials.
- Include a definition of what constitutes an adverse event in the study. For IND or IDE research include definitions as described in 21 CFR 312.32 and the ICH E2A Guidelines (<http://www.ich.org/cache/compo/475-272-1.html>).
- Describe agencies or offices to be notified with point of contact information in the event of an unanticipated problem or serious adverse event.
- All protocols should contain the following language regarding the HRPO reporting requirements for adverse events and unanticipated problems.

“Unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all volunteer deaths related to participation in the study should be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the U.S. Army Medical Research and Materiel Command’s Office of Research Protections, Human Research Protections Office. A complete written report should follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RPH, 504 Scott Street, Fort Detrick, Maryland 21702-5012”

For protocols that have a medical monitor assigned, the following language should also be included.

“The medical monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events and all volunteer deaths associated with the protocol and provide an unbiased written report of the event to the USAMRMC Office of Research Protections(ORP) Human Research Protection Office(HRPO). At a minimum the medical monitor should comment on the outcomes of the event or problem and in the case of a serious adverse event or death comment on the relationship to participation in the study. The medical monitor should also indicate whether he/she

concur with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to participation and reports of events resulting in death should be promptly forwarded to the HRPO.”

25. Continuing Review and Final Report. The protocol should acknowledge that a copy of the approved continuing review report and the local IRB approval notification will be submitted to the HRPO as soon as these documents become available. A copy of the approved final study report and local IRB approval notification will be submitted to the HRPO as soon as these documents become available.

26. USAMRMC Volunteer Registry Database. Completion of data sheets for entry into the Volunteer Registry Database is required for all greater than minimal risk intramural studies and protocols in support of Army Surgeon General-Sponsored INDs. At the discretion of the HRPO, other greater than minimal risk extramural research may be required to comply with the Volunteer Registry Database requirement. If completion of data sheets is required, a description of the Volunteer Registry Database should be included in the protocol. In addition, include the completion of the data sheets in the study procedure timelines. See section III.G.2 of this document for details regarding the Volunteer Registry Database requirement.

C. Surveys, Questionnaires, and Other Data Collection Instruments

If the research involves surveys, questionnaires, case report forms, data collection forms, rating scales, interview guides, or other instruments, include a copy of the most recent IRB-approved version of each of these documents with the protocol submission.

For each instrument that is used, the following information at a minimum should be addressed.

- Information collected with study instrument must be related to the objectives of the study
- Procedures for use of study instruments should be clear in the protocol
- Study instruments should be coded to protect confidentiality whenever possible
- For study instruments provided to and/or completed by volunteers, the study instrument should be legible, and presented at a reading level appropriate to the population. Copies of instruments submitted for review must also be legible.

D. Advertisements, Posters, and Press Releases to Recruit Volunteers

If volunteers will be recruited through an advertisement, newspaper article, or similar process, a copy of the local IRB-approved advertisement must be provided for review

and approval by the HRPO. Any “Dear Doctor” letters that will be used to aid in recruitment must also be provided for review.

For studies involving investigational drugs or devices, local IRB review of advertisements is necessary to ensure that the information is not misleading to the volunteers participating in IND studies. The FDA has established guidelines on advertisements for volunteers. General guidance includes name and address of PI, summary of research purpose, brief eligibility criteria, accurate list of benefits, and the person to contact for further information.

Some important considerations for recruitment materials include:

- Recruitment materials should not promise a cure or benefit beyond what is mentioned in the protocol or consent form.
- If the volunteers will be paid, the amount of payment should not be presented in bold type, larger than other text, or otherwise overemphasized.
- Recruitment materials should not promise “free medical treatment” when treatment is not the true intent of the study.

E. Informed Consent Document

The format of the informed consent document may vary in accordance with the requirements of the local IRB; however, the informed consent document title must be the same (or a simplified lay version) as the protocol title. The research site should be identified on the informed consent.

The informed consent document should be legible, at an adequate font size (at least 12 point is generally recommended; 14 point is preferred for elderly or visually impaired volunteers), and written at a reading level appropriate for the volunteers (the eighth grade level is recommended for adults). To improve readability use second person, short sentences, non-scientific words with less than three syllables (or define scientific words within the text), and break out text into sections.

Whenever possible the consent form should be written in the second person. (It is acceptable to use the first person at the end of the form above the volunteer’s signature with a statement such as “I have read the information above and been given an opportunity to ask questions.”) If an institution’s template requires first or third person consent forms, the HRPO will defer to the requirements of the IRB.

The document must be free from any exculpatory language through which the volunteer or representative is made or appears to waive any of the volunteer’s legal rights or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Volunteers must be provided information about the study in a language that they can understand. When there is a probability of enrolling volunteers that do not speak English, **once all recommendations have been adequately addressed and the local IRB has approved the consent form**, a copy of the consent form in the foreign language must be provided along with the English translation of the consent form. That documentation should include, on the English version, the statement, "I certify that this is an accurate and true translation," as well as the signature, name, address, phone number, and, if available, FAX number of the translator. If an approved version of an English consent form for the study is translated into a foreign language, the documentation may also be provided in the form of a letter from the translator certifying that the foreign version of the consent form is an accurate and true translation of the English consent form and include signature, name, address, phone number, and, if available, FAX number of the translator.

F. Elements to Include in the Informed Consent Document

1. Research Description. As appropriate, include the following:

- Title and Location of the Study. The title and study location must be identified and consistent with those in the protocol. Note that a lay title is acceptable on documents given to volunteers.
- Research. The consent form must make it clear that the volunteer is participating in research. If the research is incorporated into standard care, research procedures must be clearly distinguished from standard care.
- Purpose. Ensure that the purpose and objectives of the research are clearly described and accurately represented in the consent form in terms that the volunteer can understand.
- Sponsorship. Volunteers must be informed early in the consent form that the study is funded by DOD (or a specific DOD or Army organization). If the study is conducted by a military organization (e.g., intramural lab) this statement may not be necessary.
- Duration of Participation. Ensure that the duration of volunteer participation is clearly defined in the consent form. If the duration of a routine procedure will be prolonged as a result of participation, the volunteer should be informed how much extra time will be added. Estimated time taken to complete screening, questionnaires, tests, interviews, etc. should all be considered, as well as the number of visits required.
- Number of Volunteers. When appropriate, the approximate number of volunteers enrolled in the study and at each site should be present in the consent form. For example, disclosure of the number of volunteers participating in a study may be

appropriate in high risk research, in research with small numbers of volunteers, or in research where volunteers participate as part of a group.

- Procedures. The consent form must adequately describe what will be done during the course of the research project and indicate any procedures that are experimental. All tests and procedures must be described from initial screenings to follow-up. If the research is incorporated into standard care, research procedures must be clearly distinguished from standard care. The consent form should briefly explain the study design relative to what will be done to the volunteer (e.g., in blind or double-blind studies volunteers must be informed that they may receive either the experimental treatment or a placebo). If a placebo is used, its contents should be described. The consent form should specify what is required of the volunteer (hospital visits, blood donation, etc.). If blood is to be drawn, the amount(s) to be drawn and methods used to obtain the sample(s) should be expressed in lay terms.
- Precautions. When appropriate, special precautions that should be observed by the volunteer before or after the study should be clearly stated in the consent form (e.g., fasting, eating, hydration, discontinuation of, medications, caffeine, or nicotine). If the possibility exists that participation in the study may have negative effects or is a risk for a developing embryo for any period of time during and/or after participation in the study if the volunteer/partner becomes pregnant, the following statement or equivalent should be included:

“You should avoid becoming pregnant for at least (time period in days, weeks, or months) after participation in the study. To avoid becoming pregnant, you should either abstain from sexual relations or practice a method of birth control. Except for surgical removal of the uterus, birth control methods such as the use of condoms, a diaphragm or cervical cap, birth control pills, IUD, or sperm-killing products are not totally effective in preventing pregnancy.”

- Similar Studies. When available, pertinent information from previous, similar, or related studies should be provided in the consent form.

2. Risks.

- Foreseeable Risks. All reasonably foreseeable research risks must be clearly stated in the consent form. Ensure that the risks are not understated and appear prominently in the document. All reasonably foreseeable risks identified in the protocol must be included in the consent form. Reasonably foreseeable physical, psychological, emotional, social, legal, and economic risks related to participation should be considered. It is often helpful to estimate the severity and likelihood of risks and/or compare these risks with risks that the volunteer might encounter in the course of his or her daily activities. If similar research has been conducted in the past, the incidence of adverse effects or injuries occurring in the past should be included when data are available.

- Unknown Risks. When appropriate (e.g., investigational drug, device or procedure), the consent form should contain a statement that the treatment or procedure may cause risks to the volunteer (germ cells, embryo, or fetus), which are currently unforeseeable. Both men and women need to understand the danger of taking a drug whose effects on the fetus are unknown. If measures to prevent pregnancy should be taken while in the study, this should be explained in the consent form. If there is no animal data on mutagenicity and teratogenicity available for an investigational agent, the volunteer should be informed in the consent form. Also, note that pregnant women or fetuses may be involved in research (where scientifically appropriate) only if preclinical studies, including studies on pregnant animals and clinical studies, including studies on non-pregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses.
- Investigational New Drug/Device. For any protocols involving the use of an investigational new drug or device, the consent form must clearly state that the product is investigational.

3. Benefits.

- Potential Benefits. Any potential benefits that can reasonably be expected to be derived by the volunteer or others from participation in the study must be clearly stated in the consent form. Benefits identified in the consent form should be consistent with benefits identified in the protocol. If there is no direct benefit to the volunteer it must be stated in the consent form.
- Benefits Are Not Overstated. Ensure that the benefits are not overstated. Ensure that compensation is not identified as a benefit of participation.

4. Alternatives to Participation. If any appropriate alternative procedures or courses of treatment, which may be advantageous to the volunteer, are available, the alternatives must be disclosed in the consent form (for example, whether treatment is available outside the protocol). In some cases the only alternative is not to participate in the study.

5. Payment/Costs.

- Compensation. The consent form should specifically describe any payment and/or compensation that the volunteer will receive as a result of participation in the study. Any plan to pro-rate payment should a volunteer choose to withdraw should be explained. Differentials in payment among volunteer groups (e.g., military versus civilian) may require separate consent forms for each group.
- Costs. Any additional costs to the volunteer that may result from participation in the research must be stated in the consent form. Potential expenses could

include travel, parking, meals, and procedures. If research is performed simultaneously with treatment, it should be clear what procedures, medications, etc. will be billed to the volunteer or their insurance and what will be provided free of charge.

6. Medical Care for Research Related Injury. For greater than minimal risk research, institutional language describing the medical care available in the event of a research-related injury must be included.

For research conducted in USAMRMC facilities or conducted by a USAMRMC Principal Investigator (PI), the following language outlining the Army's provision for care should be inserted. See section III.G.1 for additional information on this requirement.

"If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty in the military, military spouse, or dependent), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary. This care includes but is not limited to free medical care at Army hospitals or clinics.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to free medical care for your injury at an Army hospital or clinic. It cannot be determined in advance which Army hospital or clinic will provide care. If you get care for research-related injuries outside of an Army hospital or clinic, you or your insurance will be responsible for medical expenses.

For all subjects: Transportation to and from Army hospitals or clinics will not be provided. No reimbursement is available if you incur medical expenses to treat research-related injuries. No compensation is available for research-related injuries. You are not waiving any legal rights. If you believe you have sustained a research-related injury, please contact the PI. If you have questions, please contact the PI (name and telephone number of principal investigator)."

7. Confidentiality.

- A section describing the extent to which confidentiality of records identifying the volunteer will be maintained must be included in the consent form. For example, procedures to maintain the volunteer's privacy and confidentiality must be described, including how identifying information will be stored and for how long, who will have access to the identifying data, disposition of the data, if specimens will be maintained and for how long.
- It should be noted in the consent form that representatives of the local IRB and the USAMRMC are eligible to review research records as a part of their responsibility to protect human volunteers in research. For investigational drug or device studies a statement that the FDA and the sponsor (if applicable) may

review the records should be included. In the event that a HIPAA authorization is required, include the representatives of USAMRMC as one of the parties to whom private health information may be disclosed.

8. Participation and Withdrawal.

- Voluntary Participation. The consent form must contain a statement that participation is voluntary. Refusal to participate will involve no penalty or loss of benefits, and the volunteer may withdraw at any time without penalty or loss of benefits.
- Volunteer Withdrawal. The consent form must describe the consequences of a volunteer's decision to withdraw and procedures for the orderly end of a volunteer's participation. Volunteers must be allowed to withdraw at any time. If withdrawal results in any decrease in promised compensation, this must be justified and described in the consent form. When withdrawal from the study may have deleterious effects on the volunteer's health or welfare, the consent form should explain any withdrawal procedures that are necessary for the volunteer's safety and specifically state why they are important to the volunteer's welfare. The consent form should also state whether withdrawal of samples/data will be possible.
- Early Termination of Research. The consent form must inform the volunteer of any anticipated circumstances under which the volunteer's participation may be terminated by the investigator, study sponsor, or others without regard to the volunteer's consent. Potential circumstances under which this might occur include:
 - Adverse reaction/condition occurs and it might be dangerous or detrimental to the volunteer's health to continue.
 - The volunteer fails to keep study visits as explained or does not follow the instructions given by the investigator.
 - Limitations on the availability of the treatment.
 - Other medical events.
 - Protocol violation or early closure of the study.
- Significant New Findings. As appropriate, the consent form should state that any significant new findings developed during the course of research, which may relate to the volunteer's willingness to continue participation, will be provided.

9. Contact Information. If multiple sites are involved, a local contact should be given as well as the contacts at the main study site whenever possible.

- Research Information. Ensure that the consent form indicates whom to contact with questions about the research, including name or office and telephone numbers. For studies enrolling volunteers from a large geographic area at one site, a toll free number is recommended. An example of an appropriate individual is the PI.
- Volunteers' Rights. Ensure that the consent form indicates whom to contact with questions about volunteers' rights including name or office and telephone numbers. Appropriate examples include the local IRB or Ethics Committee or a patient's advocate.
- Research Related Injury. Ensure that the consent form indicates whom to contact in the event of a research-related injury, including name or office and telephone numbers. Examples of appropriate individuals include the PI, Medical Monitor, and the legal office.
- PI. Ensure that the consent form contains contact information for the PI (if not addressed above), including name and telephone number.

10. Volunteer Registry Database. All studies that require completion of volunteer registry data sheets must notify volunteers of the Volunteer Registry Database requirement in the consent form. The following statement is suggested for inclusion in the "Confidentiality" section of the consent form:

"It is the policy of the USAMRMC that data sheets are to be completed on all volunteers participating in research for entry into this Command's Volunteer Registry Database. The information to be entered into this confidential database includes name, address, social security number, study name, and dates. The intent of the data base is twofold: first, to readily answer questions concerning an individual's participation in research supported by the USAMRMC; and second, to ensure that the USAMRMC can exercise its obligation to ensure research volunteers are adequately warned (duty to warn) of risks and to provide new information as it becomes available. The information will be stored at the USAMRMC for a minimum of 75 years."

See section III.G.2 for additional information on the Volunteer Registry Database Requirements.

11. Documentation.

- Signature of Volunteer. The consent form should contain spaces to record the printed or typed name and signature of the volunteer or the LAR and date.

- Signature of Witness. When appropriate, the consent form should contain spaces to record the printed or typed name and signature of the witness to the consent process and date in accordance with 32 C.F.R. § 219.117(b)(2).
- Consent for Testing for Communicable Diseases. If the research will involve screening for reportable communicable diseases (e.g. HIV, hepatitis, tuberculosis, sexually transmitted diseases (STDs)) separate consent should be given for the test. Documentation of consent may be addressed in the body of the consent form or as a separate consent form in accordance with the state/jurisdiction in which the study is being conducted. Risks associated with a positive result must be disclosed. State requirements for reporting must be disclosed and provisions taken to maintain confidentiality described.
- Possible Sample Donation/Commercial Products. If any samples will be collected and stored for use in future research, the following language or the equivalent should appear in the consent form. Volunteers should be given the option to participate in the study without donating their tissue. A separate sample donation form can be used but is not required. Language describing how the volunteer's confidentiality will be maintained, how long the samples will be retained, and who will have access to the samples should be included.

Note: This is sample language. Institutions may use their own template language to address sample donation.

During this study you will be asked to provide _____ (clearly specify the type of samples to be provided). These samples will be used for _____ (enter all known and anticipated uses) and may also be used for purposes that are currently unknown. There is a chance that the samples that you are donating under this study may be used in other research studies and may have some commercial value. (If a commercial value is anticipated, that value should be clearly described at this point). Should your donated sample(s) lead to the development of a commercial product, _____ will own it and may take action to patent and license the product. _____ does not intend to provide you with any compensation for your participation in this study nor for any future value that the samples you have given may be found to have. You will not receive any notice of future uses of your sample(s). (When the study involves treatment as well as research, the following language should be added: You may agree to participate in the research protocol but refuse to provide the additional samples discussed above.)

_____ Samples can be stored for future use.

_____ Samples to be used in the current study only. Samples cannot be stored for future use

M. Supportive Materials. Any materials used to supplement the consent form should be reviewed, which may include information sheets, videos, briefing slides, visit schematics, and other materials.

Section 3

VI. Where to Go for Help and Information

Investigators requiring assistance with research involving human subjects should first contact the local IRB for institutional requirements. Investigators should also consult the guidance provided in this document while preparing submissions to the local IRB, as the HRPO will need to review and approve the same documents that are reviewed and approved by the local IRB. Documents should be prepared to meet both local and USAMRMC ORP HRPO requirements to avoid delays in approval. Specific guidelines are subject to change as governing regulations, policies, and procedures are updated.

For questions regarding the USAMRMC ORP HRPO protocol and consent form requirements or the review and approval process, contact the HRPO at the address or phone number listed below.

Phone: 301-619-6987

Mail: Commanding General, U.S. Army Medical Research and Materiel Command
ATTN: MCMR-RPH
504 Scott Street
Fort Detrick, MD 21702-5012

E-mail: hsrrb@amedd.army.mil

References:

- Title 32 Code of Federal Regulations, Part 219, Protection of Human Subjects
- Title 21 Code of Federal Regulations, Part 50, Protection of Human Subjects
- Title 21 Code of Federal Regulations, Part 56, Institutional Review Boards
- Title 21 Code of Federal Regulations, Part 312, Investigational New Drug Application
- Title 21 Code of Federal Regulations, Part 812, Investigational Devices
- Title 45 Code of Federal Regulations, Part 46, Subparts A, B, C, and D, Protection of Human Subjects
- Code of Federal Regulations is located at <http://www.gpoaccess.gov/cfr/index.html>
- Army Regulation 70-25, Use of Volunteers as Subjects of Research
- Army Regulation 40-7, Use of Investigational Drugs and Devices in Humans and the Use of Schedule I Controlled Drug Substances
- Army Regulations can be located at <http://www.usapa.army.mil>
- Title 10 United States Code, Section 980
- Department of Defense Directive 3216.02
- International Conference on Harmonisation, Good Clinical Practice, Consolidated Guideline is located at <http://www.fda.gov/cder/guidance/959fnl.pdf>; all other ICH guidelines can be found in the ICH home page located at <http://www.ich.org/cache/compo/276-254-1.html>

Copies of the preceding references can be obtained from either the U.S. Government Printing Office or the National Technical Information Service at:

Phone: 202-512-1800

Web Site: <http://www.gpoaccess.gov/index.html>

Mail: Superintendent of Documents
P.O. Box 371954
Pittsburgh, PA 15250-7954

Phone: 703-605-6000; 800-553-NTIS

E-mail: orders@ntis.fedworld.gov

Mail: National Technical Information Service
5285 Port Royal Road
Springfield, VA 22161

VII. Appendices

Appendix A - Claim of Exemption From Review by the USAMRMC Office of Research Protections (ORP), Human Research Protection Office (HRPO)

PROTOCOL TITLE:	
PRINCIPAL INVESTIGATOR'S NAME:	PROPOSAL NO:
INSTITUTION:	

COMPLETE THIS SECTION IF YOU ARE REQUESTING PERMISSION TO STUDY EXISTING DATA, DOCUMENTS, RECORDS, AND/OR BIOLOGICAL SPECIMENS (EXEMPTION UNDER CATEGORY 32 CFR 219/45 CFR 46.101(b)(4). EACH QUESTION MUST BE COMPLETED.

1. Will existing or archived human data, documents, medical records, database records and/or biological specimens be used? (Note: Data or biological specimens are considered to be "existing" or "archived" if all the data/biological specimens to be used for the research have been collected prior to the submission of this exemption application.)	Yes	No
2. What is/are the (a) type and (b) source of the data/biological specimens? Provide detailed and specific information. Provide a copy of any surgical/donation consent forms used for obtaining data/biological specimens. Use an additional page if needed.		
<hr/> <hr/> <hr/> <hr/>		
3. Were data/biological specimens originally collected solely for research purposes? If yes is checked, please attach a copy of the IRB-approved Consent Form for the research under which the original data/biological specimens were collected.	Yes	No

**Appendix A - Claim of Exemption From Review by the USAMRMC Office of
Research Protections (ORP), Human Research Protection Office (HRPO)
(Continued)**

4. Is the source of the data/biological specimens publicly available?	Yes	No
5. How are the data/biological specimens identified when they are made available to you/your study team? Indicate by marking the appropriate box: a. <input type="checkbox"/> Direct identifier (e.g., subject name, address, social security number, medical record number, etc.) b. <input type="checkbox"/> Indirect identifier (e.g., an assigned code which could be used by the investigator or the source providing the data/biological specimens to identify a subject such as a pathology tracking number or tracking code used by the source) c. <input type="checkbox"/> No identifier (i.e., neither the researcher nor the source providing the data/biological specimens can identify a subject based upon information provided with the data/biological specimens) d. <input type="checkbox"/> Other – please explain _____ _____		
6. If 5.a or 5.b is checked above and you are requesting permission to study biological specimens, will the identifier(s) provided with the specimens be removed and destroyed upon receipt by your study team?	Yes	No*
7. If 5.a or 5.b is checked above and you are requesting permission to study archived data, will you abstract and record any subject identifiers as a part of the data collection process?	Yes*	No
8. Did the IRB of record determine that the research qualifies for exemption from the requirements of the regulations for the protections for human subjects? (Provide a copy of the IRB of record's determination memo and/or OMB Form 0990-0263.)	Yes	No
*The research protocol does not qualify for exemption from the requirements at 32 CFR 219/45 CFR 46.		

**Appendix A - Claim of Exemption From Review by the USAMRMC Office of
Research Protections (ORP), Human Research Protection Office (HRPO)
(Continued)**

<p>COMPLETE THIS SECTION IF YOU ARE REQUESTING EXEMPTION UNDER CATEGORIES 32 CFR 219/45 CFR 46.101(b)(1) and/or (2)</p>

1. Does the research involve children?	Yes	No
2. Is the research conducted in established or commonly accepted educational settings?	Yes	No
3. Does the research involves normal educational practices?	Yes	No
4. Is this research on regular and/or special education instructional strategies? Describe	Yes	No
5. Is this research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods? Describe	Yes	No
6. Does the research involve any of the following? Educational tests (cognitive, diagnostic, aptitude, achievement) _____ Survey procedures _____ Interview procedures _____ Observation of public behavior _____ Provide copies of all instruments.	Yes	No
7. Would any disclosure of the participants' responses outside the research reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation?	Yes	No
8. Will the information obtained be recorded in such a manner that participants can be identified directly or indirectly through identifiers linked to the participants?	Yes	No

**Appendix A - Claim of Exemption From Review by the USAMRMC Office of
Research Protections (ORP), Human Research Protection Office (HRPO)
(Continued)**

9. Does the research involve prisoners?	Yes	No
10. Did the IRB of record determine that the research qualifies for exemption from the requirements of the regulations for the protections for human subjects? (Provide a copy of the IRB of record's determination memo and/or OMB Form 0990-0263.)	Yes	No

Investigator's Statement

The undersigned certifies that the information provided in this document is complete and correct. Any modifications to this research that (a) change the research in a substantial way or (b) might change the basis for exemption will be provided to the IRB of record and the USAMRMC ORP HRPO for review to ensure that the exemption is still valid.

Principal Investigator's Signature

Date

Appendix B - Protocol Submission Checklist

PROTOCOL TITLE:	
PRINCIPAL INVESTIGATOR'S NAME:	PROPOSAL NO:
INSTITUTION:	

Requirements for All Protocols as Appropriate:

- Research Protocol
- Consent/Assent/HIPAA Authorization Form(s)
- Curriculum Vitae* or Biosketch for Principal Investigator and Medical Monitor
- Documentation of the Human Research Ethics Training (within 3 years) for the Principal Investigator, Co-investigators, and the Medical Monitor
- Scientific Review/Peer Review Approval(s)
- Letter from the IRB with the following information: (a) risk level that the IRB classified the protocol (exempt, NGTMR, GTMR); (b) date of IRB approval; (c) next continuing review date; (d) any waivers approved; and (e) risk for medical devices (non-significant risk or significant risk)
- Recruitment Materials, e.g., advertisements, posters, and announcements, recruitment letters, phone scripts, briefing materials
- Study Instruments (e.g. questionnaires, interview guides, etc.), case report form(s), data collection/recording form(s)
- Additional Committee and Regulatory Approvals, e.g., Radiation Control Committee, Institutional Biosafety Committee, RAC review, FDA letters
- Other Documents Signed by the Subject, e.g., Procedural Consent Forms, Sample Donation Forms, Consent for Testing or Communicable Diseases, Photo Release Form, Future Contact Form
- Completed Conflict of Interest Forms

Additional Requirements for IND or Device Protocols:

- Document specifying IND/IDE Number
- Investigator's Brochure or Manufacturer's Device Manual/device information
- A signed Form FDA 1572

Appendix B - Protocol Submission Checklist (Continued)

___ Document from manufacturer declaring level of risk for device (non-significant risk or significant risk) and IDE form

___ Documentation of the Investigator's most recent GCP training (if available)

Type of study is proposed (i.e., Phase I trial, pilot study, laboratory experiment, intervention, survey/record review, longitudinal, retrospective, etc.)

Procedures to be performed (Administration of experimental drug, collection of biological specimens, diagnostic procedures, procedures involving radiation or radioactive materials, etc.)

Drug (s) to be used: _____ Drug Type: _____

Volunteer Information:

Age range: _____ Gender: ___Male ___Female

Total number of volunteers expected to be enrolled: _____

Total number of volunteers at each collaborating site: _____

Are volunteers able to provide their own consent? ___Yes ___No

Vulnerable Class: ___Prisoners ___Minorities ___HIV positive ___Psychologically impaired
___Impaired decision-making ___Psychiatric patient ___Military ___Employee/Student ___Trauma

Volunteer Recruitment: ___Paid volunteers ___Out-patients ___Students/employees
___In-patients

Principal Investigator's Signature

Appendix C - Multi-Site Protocol Submission Checklist

_____ Federalwide or DOD Assurance Number for awardee and each research site

_____ IRB Approval Letter from an IRB listed on assurance for awardee and each research site (or appropriate IRB authorization agreement)

_____ Site-Specific Protocol Addendum describing site specific implementation of the protocol (including, but not limited to, recruitment, informed consent, differences in research procedures, optional procedures, handling and transport of specimens and data, site reporting requirements). A description of any unique aspects to the study population at the site should be included (for example, low socioeconomic status, non-English speaking, cultural or religious beliefs, illegal immigrants, etc.).

_____ Site-specific Consent/Assent/HIPAA Authorization Forms

_____ Site-Specific Recruitment Materials

_____ CV/Biosketch for the Principal Investigator, Co-Investigator(s), and Medical Monitor (if applicable) at each site

_____ Human Research Ethics Training for the Principal Investigator, Co-Investigator(s), and Medical Monitor (if applicable) at each site

_____ Conflict of Interest Forms for Key Research Personnel at each site

_____ For IND protocols, signed FDA Form 1572

Appendix D - Exempt Protocol Checklist

NOTE: All proposals must contain: (1) a detailed proposal or protocol (if essentially the same) or a detailed protocol if different from the proposal; (2) Scientific Review/Peer Review; and (3) *Curriculum Vitae* (CV) of the Principal Investigator (PI) or a Bio-Sketch.

Exempt Protocol Checklist*:	Yes	No	N/A
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Human Anatomical Substances Used

REQUIRED Claim of Exemption form	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
REQUIRED Local IRB Letter of Exemption or Optional form 310 (Signed by IRB Chair or designee)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Supporting Letters of Collaboration/Agreement from Human Anatomical Substance Repositories indicating what personal identifying information, if any, will be released.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
If applicable, Consent Form used for donation of tissues for research	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Educational Practices/Tests/Surveys Used

REQUIRED Claim of Exemption form	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
REQUIRED Local IRB Letter of Exemption or Optional form 310 (Signed by IRB Chair or designee)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Supporting Letters of Collaboration/Agreement from Educational Agency/ies	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Copies of all written tests, interview questions, surveys, and/or data collection instruments	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Existing Data/Documents/Records Used

REQUIRED Claim of Exemption Form	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
REQUIRED Local IRB Letter of Exemption or Optional Form 310 (Signed by IRB Chair or designee)	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Appendix D - Exempt Protocol Checklist (Continued)

- | | | | |
|--|--------------------------|--------------------------|--------------------------|
| Supporting Letters of Collaboration/Data Use Agreements from Agencies that maintain the data/documents/records indicating what personal identifying Information, if any, will be used. | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| Data collection procedures to include instruments | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |
| HIPAA Authorization or waiver when data/documents/ records used are from a covered entity | <input type="checkbox"/> | <input type="checkbox"/> | <input type="checkbox"/> |

*Based on the scope of the project, other documents may be requested or required.

Appendix E - Commonly Applied Exemption Categories from the Human Subjects Protection Regulations at 32 CFR 219/45 CFR 46

Exemption Category number	Information	Involves the following:	Does NOT involve the following:	Additional comments
101(b)(1)	The research is conducted in established or commonly accepted educational settings. The research involves normal educational practices.	<p>Research on regular and special education instructional strategies.</p> <p>Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.</p>	<p>The research does not involve prisoners as participants.</p> <p>The research is not FDA-regulated.</p>	
101(b)(2)	If any disclosure of the participants' responses outside the research could reasonably place the participants at risk of criminal or civil liability or be damaging to the participants' financial standing, employability, or reputation, the information obtained may not be recorded in such a manner that participants can be identified, directly or indirectly through identifiers linked to the participants.	<p>Educational tests (cognitive, diagnostic, aptitude, achievement)</p> <p>Survey procedures</p> <p>Interview procedures</p> <p>Observation of public behavior</p>	<p>The research does not involve prisoners as participants.</p> <p>The research is not FDA-regulated.</p>	<p>If the research involves children as participants, the procedures do not involve any of the following:</p> <p>Survey procedures</p> <p>Interview procedures</p> <p>Observation of public behavior where the investigators participate in the activities being observed</p>

Appendix E - Commonly Applied Exemption Categories from the Human Subjects Protection Regulations at 32 CFR 219/45 CFR 46 (Continued)

Exemption Category number	Information	Involves the following:	Does NOT involve the following:	Additional comments
101(b)(4)	Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens.	The sources are publicly available Or the investigator records information in such a manner that participants cannot be identified directly or indirectly through identifiers linked to the participants.	The research does not involve prisoners as participants. The research is not FDA-regulated.	Data or biological specimens are considered to be “existing” or “archived” if all the data/biological specimens to be used for the research have been collected prior to the submission of the exemption application.

Appendix F - USAMRMC Human Research Protection Office Continuing Review Submission Checklist

REQUIRED DOCUMENTS

- The continuing review summary report that was submitted to your IRB.
- Local IRB approval letter with next expiration date.
- Current copy of protocol. List or track all amendments that have occurred since the last time the protocol was submitted to HRPO.
- Current consent form, if applicable. List or track all revisions that have occurred since the last time the consent form was submitted to HRPO.

The following checklist is provided as guidance regarding the required elements to be included in a continuing review report. Please ensure that applicable items are addressed in the continuing review report or attached in a separate document:

- Total number of subjects that gave informed consent for, were withdrawn from, are currently taking part in, and/or completed the study.
- For studies employing consent waivers, total number of samples collected or participants records accessed.
- Breakdown of participants by demographics as appropriate (e.g., groups/cohorts, gender, age, ethnicity, special populations).
- Summary of all adverse events (including SAEs) and unanticipated problems involving risks to subjects or others
- Summary of withdrawals that have occurred with reasons for withdrawal (i.e. screen failures, withdrawn by PI, discontinuation by subject, dis-enrolled [deaths, other]).
- Summary of complaints received.
- Summary of deviations that have occurred.
- Report includes a summary of research progress including results obtained to date.
- Documentation of literature review update including databases searched, dates of searches, key words, and subject areas searched. Risk/benefit assessment or other protocol activities updated as necessary based on review of literature. Measures included to reduce or minimize any newly identified risks.
- Summary of all amendments, addendums, or modifications that have been made to the protocol since the last approval by HRPO (administrative, minor and major changes). The revisions can be submitted on a tracked document or a separate memo.

Appendix H - Exemption Categories

The following list, taken from 32 CFR 219.101, details the exemption categories.

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

Appendix H - Exemption Categories (Continued)

- c. Possible changes in or alternatives to those programs or procedures, or
 - d. Possible changes in methods or levels of payment for benefits or services under those programs.
6. Taste and food quality evaluation and consumer acceptance studies,
- a. If wholesome foods without additives are consumed, or
 - b. If a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the FDA or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

Appendix I - Categories of Research that Qualify for Expedited Review

1. Clinical studies of drugs for which an Investigational New Drug (IND) application is not required or of medical devices for which an Investigational Device Exemption (IDE) application is not required or the medical device has been cleared/approved for marketing and the device is being used for its cleared/approved labeling.
2. Collection of blood samples by finger, heel or ear stick, or by venipuncture in healthy non-pregnant adults who weigh at least 110 pounds where the amount of blood drawn does not exceed 550 mL in an 8-week period and collection does not occur more frequently than two times per week. Collection of blood samples by finger, heel, or ear stick or by venipuncture in other adults or children where the amount of blood drawn may not exceed the lesser of 50 ml or 3 ml/kg in an eight week period and collection does not occur more frequently than two times per week.
3. Prospective collection of biological specimens for research purposes by noninvasive means, such as hair and nail clippings, teeth extracted as routine patient care, excreta and external secretions, saliva, placenta removed at delivery, amniotic fluid obtained at the time of membrane rupture or during labor, dental plaque and calculus that is not more invasive than routine care, mucosal and skin cells collected by buccal scraping, mouthwashings or swab, and sputum.
4. Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays and microwaves.
5. Research involving materials, such as data, documents, records or specimens, that have been collected or will be collected solely for non-research purposes (e.g., medical treatment or diagnosis).
6. Collection of data from voice, video, digital, or image recordings made for research purposes.
7. Research on individual or group characteristics or behavior or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation or quality assurance methodologies.

Appendix J - Criteria for Waiver of Informed Consent, Consent Documentation, and HIPAA

A. Criteria for Waiver of Informed Consent

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

B. Criteria for Waiver of Documentation of Informed Consent

1. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
2. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context.

C. Criteria for Waiver of HIPAA Authorization

1. The use or disclosure of the PHI involves no more than minimal risk to the privacy of individuals based on, at least, the presence of the following elements:
 - a. An adequate plan to protect health information identifiers from improper use and disclosure.
 - b. An adequate plan to destroy identifiers at the earliest opportunity consistent with conduct of the research (absent a health or research justification for retaining them or a legal requirement to do so).
 - c. Adequate written assurances that the protected health information (PHI) will not be reused or disclosed to (shared with) any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the PHI would be permitted under the Privacy Rule.
2. The research could not practicably be conducted without the waiver or alteration.
3. The research could not practicably be conducted without access to and use of the PHI.

Appendix K - Requirements for Reporting Serious Adverse Events and Unanticipated Problems to the USAMRMC Office of Research Protections Human Research Protection Office

The Human Subjects Protection Regulations at 32 CFR 219 and 45 CFR 46 require that Institutional Review Boards (IRBs) have written procedures for ensuring prompt reporting to the IRB, institutional officials, and the department or agency head any unanticipated problems resulting in risks to subjects or others. IRBs are responsible for determining what is meant by “prompt,” developing an appropriate reporting procedure, and communicating this procedure to those engaged in research within the IRB’s purview. Reporting procedures will differ from institution to institution, so it is important for investigators to identify the reporting requirements for all entities involved in review of the protocol and to clearly define this procedure within the protocol.

Unanticipated problems resulting in risk to volunteers or others encompass more than what one usually thinks of as adverse events. “Problems involving risk” may not necessarily result in harm. For example, misplacing a volunteer’s study records containing identifiable private information can result in the risk of breach of confidentiality. Confidentiality may or may not be breached, but either way this would be a reportable event. Another example would be administering the wrong agent to a volunteer at one time point in a series of vaccinations. Risks to others must also be reported. For example, an inadvertent exposure of a household contact in a smallpox vaccine trial would be a reportable event. Problems resulting in risks to members of the research team are also reportable.

Unanticipated problems are those problems that are not described in the protocol or other study documents. The USAMRMC ORP HRPO policy for Reporting of Unanticipated Problems on the HRPO website provides a sample reporting form that includes all of the elements required to be reported. Investigators may use this form if there is no equivalent available at their local institution. If the institutional form or study specific form does not contain all of the elements contained on the USAMRMC ORP HRPO reporting form, additional information may be requested from the investigator by the HRPO staff. For adverse drug experiences, submission of a Medwatch form is acceptable.

For serious adverse events, include in the initial adverse event report the name of the person submitting the report, if different from the PI, name of the study, the HRPO log number (A-xxxxx) assigned to the study, the number of volunteers enrolled to date, and the number and type of serious and unexpected adverse events previously reported in the study.

If the adverse event occurs in an IND study, the initial report must be identified as the “Initial Report for Volunteer (# or initials) enrolled in the clinical study “Title” and Log Number A-XXXX under IND #.”

**Appendix K - Requirements for Reporting Serious Adverse Events and
Unanticipated Problems to the USAMRMC Office of Research Protections Human
Research Protection Office (Continued)**

The following information must be provided:

- a. Description of Study. Double or single blind. If the study is being conducted in phases, indicate what phase of the study the volunteer is participating in.
- b. Number of volunteers enrolled. Total number of volunteers enrolled at the time of the adverse event.
- c. Synopsis of event. Provide a complete narrative of the event.
- d. Volunteer status. Did the volunteer recover? What was the patient status at the time of the report?
- e. Other serious and unexpected adverse events from this study. Please provide any information pertaining to other adverse events that may have occurred during the conduct of this study.
- f. Most frequently expected adverse events based on the nature of the product. What adverse events would be expected based on the nature of the product or based on information contained in the most current version of the Investigator's Brochure.
- g. Actions taken in response to the adverse event. Is the volunteer still enrolled in the study or not? Were any modifications or changes made to the protocol in response to the event? Provide an assessment of the relationship of the adverse event/s to the volunteer's participation in the study.
- h. Submit identification information for the individual completing the report. Include the signature, printed name and role identification for the study (i.e., investigator, study physician, etc.)

For studies with a medical monitor assigned, the Investigator must inform the medical monitor of any unanticipated problems or serious adverse events. A medical monitor report that comments on the outcomes of the event and the relationship of the event to participation in the study must be submitted to the HRPO within ten calendar days. The medical monitor should indicate whether he/she concurs with the details provided in the Investigator's report. Follow-up reports should be submitted until resolution of the unanticipated problem. Appropriate supporting documents, such as laboratory reports, pathology reports, and discharge summaries, should be submitted with the unanticipated problem or serious adverse event report.

**Appendix K - Requirements for Reporting Serious Adverse Events and
Unanticipated Problems to the USAMRMC Office of Research Protections Human
Research Protection Office (Continued)**

The HRPO will evaluate reported information to determine if changes are warranted in the research protocol or protocol-related documents or in the information provided to volunteers. Any changes required by the local IRB should be communicated immediately to the HRPO.

The following reporting requirement applies to all greater than minimal risk protocols. The HRPO may require the language to appear in the protocol:

“All unanticipated problems involving risk to subjects or others, serious adverse events related to participation in the study, and related subject deaths will be promptly reported by phone (301-619-2165), by e-mail (hsrrb@amedd.army.mil), or by facsimile (301-619-7803) to the HRPO. A complete written report will follow the initial notification. In addition to the methods above, the complete report can be sent to the U.S. Army Medical Research and Materiel Command, ATTN: MCMR-RPH, 504 Scott Street, Fort Detrick, Maryland 21702-5012.”

Protocols with a medical monitor assigned should also include the following information:

“The medical monitor is required to review all unanticipated problems involving risk to volunteers or others, serious adverse events related to participation in the study and all volunteer deaths associated with the protocol and provide an unbiased written report of the event to the USAMRMC Office of Research Protections (ORP) Human Research Protection Office (HRPO). At a minimum the medical monitor should comment on the outcomes of the event or problem and, in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor must also indicate whether he/she concurs with the details of the report provided by the principal investigator”.