

**Headquarters, United States Army
Medical Research and Materiel Command
(HQ USAMRMC)**

**Office of Research Protections
Institutional Review Board Office**

HQ USAMRMC Institutional Review Board

Policies and Procedures

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Chapter 1. Introduction

1-1. Purpose

These written policies and procedures establish the operational guidelines for effective functioning of the Headquarters, U.S. Army Medical Research and Materiel Command Institutional Review Board (HQ USAMRMC IRB) in full compliance with the federal, Department of Defense (DOD), United States Army (Army), USAMRMC, state and international human subjects protection regulatory requirements.

1-2. References

Related references are listed in Appendix A.

1-3. Definitions

Definitions for terms used in this document are provided in Appendix B.

1-4. Explanation of abbreviations

Abbreviations and terms used in this document are explained in the Glossary.

1-5. Overview

a. The Army and the Army Medical Command (MEDCOM) are strongly committed to ensuring the protection of human subjects participating in research. The U.S. Army Medical Research and Materiel Command (USAMRMC), the Army Regional Medical Commands, and Military Treatment Facilities (MTFs) are institutions responsible for conducting, contracting, sponsoring, supporting or managing a majority of the Army's human biomedical and socio-behavioral research. As such these institutions are entrusted with the responsibility to protect the human participants involved in Army research.

b. The Secretary of the Army, as the head of a DOD Component has delegated the authority and responsibilities set forth in DOD Directive 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DOD Supported Research," paragraph 5.3 to the Army Surgeon General (TSG). The Army Surgeon General serves as the authority and assumes responsibility within the Army to provide regulatory oversight of all research involving human subjects regardless of the source of funding or the command, staff or agency conducting the research. The Director, Defense Research and Engineering (DDR&E) delegated the authority to approve DOD assurances and accept other federal assurances for all institutions conducting human subjects research on behalf of the Army to the Army Surgeon General. The Army Surgeon General has delegated the authority to approve DOD Assurances to the Assistant Surgeon General, Force Projection (ASG, FP). The Army Surgeon General has delegated the authority to accept other federal Assurances to the ASG, FP and the Commanding General (CG), USAMRMC. The Army Surgeon General has also delegated authority to approve USAMRMC and non- Army Medical Department (AMEDD) Army research involving human subjects to the CG, USAMRMC.

c. The Army Human Research Protections Office (AHRPO) was established on 1 August 2006 to manage the U.S. Army Human Research Protection Program (HRPP) under the

oversight of the ASG, FP. The AHRPO is responsible to ASG, FP and TSG for regulatory oversight of all human subject research conducted or supported by the Army.

d. The USAMRMC Office of Research Protections (ORP) is the USAMRMC Headquarters (HQ) element charged with ensuring that USAMRMC conducted, contracted, sponsored, supported or managed research and AMEDD clinical investigations involving human subjects, human anatomical substances or animals are conducted in accordance with (IAW) federal, DOD, Army, USAMRMC, state and international regulatory requirements.

e. All non-exempt human subjects research conducted or supported by the Army (and DOD) must be reviewed and approved by a duly constituted Institutional Review Board (IRB); the HQ USAMRMC IRB provides this review and oversight for the organizations described in Chapter 2 of this document. The HQ USAMRMC IRB Office is a subordinate office within the ORP, and administers activities of the HQ USAMRMC IRB.

f. These policies and procedures describe how the USAMRMC ORP and HQ USAMRMC IRB operationalize the federal, DOD, Army, USAMRMC, state and international regulatory requirements for human subjects protection. These policies and procedures apply to the HQ USAMRMC IRB, the ORP IRB Office and all organizations and personnel for whom the HQ USAMRMC IRB serves as IRB.

Chapter 2. HQ USAMRMC IRB's Review Authority and Scope of Services

2-1. Authority

a. Federal Regulations. The human subjects protection regulations at Title 32, Code of Federal Regulations (CFR), Part 219, the "Common Rule;" 45 CFR 46, Subparts B, C and D; and 21 CFR 50 and 56 set forth the requirements for review of non-exempt human subjects research by an IRB. The HQ USAMRMC IRB provides human subjects protection review, approval and oversight of protocols IAW these regulations.

b. Department of Defense Directive (DODD) 3216.02. DODD 3216.02, "Protection of Human Subjects and Adherence to Ethical Standards in DOD Supported Research," establishes the DOD's commitment to ensuring that the rights and welfare of human subjects in research supported or conducted by the DOD Components are protected. This protection encompasses basic respect for persons, beneficence, and justice in the selection of subjects. The Directive implements 32 CFR 219 and its requirements for all non-exempt research involving human subjects to be reviewed and approved by an IRB.

c. Purpose of the HQ USAMRMC IRB. The HQ USAMRMC IRB serves as a component of the USAMRMC HRPP. The primary purposes of the IRB are:

(1) To protect the safety, rights, and welfare of participants in research that is under the purview of the HQ USAMRMC IRB.

(2) To serve as a safeguard to prevent the unethical treatment of humans in research that might lead to physical, psychological, social, or other harms.

(3) To assure that the design and conduct of research involving human subjects complies with applicable federal, DOD and USAMRMC regulatory requirements.

2-2. Scope of IRB Services

The HQ USAMRMC IRB provides IRB services for:

(1) Scientists Assigned to HQ USAMRMC. The HQ USAMRMC IRB serves as the IRB of Record for scientists who conduct human subjects research and are assigned to the HQ USAMRMC. The HQ USAMRMC consists of the Command Group, the Principal Assistants for Science and Technology and Acquisition, the Personal Staff, the Special Staff, the Coordinating Staff, the Liaison Elements, and Directors and the Research Area Directorates that include the Military Infectious Disease Program, Combat Casualty Care, Military Operational Medicine, Clinical and Rehabilitative Medicine, the Congressionally Directed Medical Research Programs, and the Telemedicine and Advanced Technology Research Center.

b. The USAMRMC Subordinate Institutes and Laboratories. The HQ USAMRMC IRB serves as the IRB for the U.S. Army Aeromedical Research Laboratory, the U.S. Army Institute of Surgical Research, and the U.S. Army Medical Research Institute of Chemical Defense. Additionally, the HQ USAMRMC IRB serves as an IRB of Record on an ad hoc, per protocol basis for USAMRMC Institutes and Laboratories with their own IRBs. The division of responsibilities for human research protections is delineated in DOD Institutional Agreements for IRB Review between the USAMRMC Institute or Laboratory and the HQ USAMRMC.

c. United States Central Command (USCENTCOM). The HQ USAMRMC IRB serves as the IRB for human research conducted within the USCENTCOM area of operations. The division of responsibilities for human research protections is delineated in the DOD Institutional Agreement for IRB Review between the USCENTCOM and the HQ USAMRMC and further detailed in the USCENTCOM HRPP plan.

d. Non-USAMRMC DOD institutions. The HQ USAMRMC IRB serves as the IRB for DOD institutions outside the USAMRMC and select civilian institutions receiving DOD human subjects research funding. The HQ USAMRMC IRB provides the required initial and continuing review and oversight of human subjects research protocols for these institutions. For these institutions, the division of responsibilities for human research protections is delineated in the DOD Institutional Agreements for IRB Review and in Memoranda of Agreement or Understanding with the respective institutions.

e. Force Health Protection (FHP) Investigational New Drug (IND) Protocols. The HQ USAMRMC IRB is designated as the IRB of Record for review and approval of the DOD contingency IND protocols for FHP. Refer to Chapter 14 of this document for information regarding the HQ USAMRMC IRB's role in the review of contingency IND protocols for FHP.

f. Central IRB. As part of an effort to improve the efficiency of IRB review(s) for collaborative and multi-site research, the HQ USAMRMC IRB may serve as a central IRB for research conducted at multiple DOD MTFs and/or USAMRMC Institutes and Laboratories. For these protocols, the division of responsibilities for human research protections is delineated in the DOD Institutional Agreements for IRB Review and/or in Memoranda of Agreement or Understanding with the respective institutions.

Chapter 3. Human Subjects Protection Education & Training Requirements

3-1. Background

Human subjects protection training and continuing education is critical to ensure that research is conducted in an ethical manner and that subjects' safety, rights, autonomy, and welfare are protected.

a. All personnel subject to this policy who conduct, review, approve, support, manage, or oversee research for which the HQ USAMRMC IRB serves as the IRB of record, must complete initial human subjects research ethics training prior to beginning their relevant duties involving human subjects research, and must also complete continuing education every three (3) years, depending on their roles and responsibilities in human subject research.

b. In lieu of the training described below, the HQ USAMRMC IRB may accept documentation of comparable and equivalent human subjects protection training and continuing education for investigators, key research personnel, and medical monitors whose institutions have established requirements for this training.

c. Regulatory Basis for Training Requirements.

(1) DODD 3216.02, "Protection of Human Subjects," requires:

(a) that awareness of human subjects protection requirements be established for all DOD personnel involved in the conduct, review, or approval of research involving human subjects;

(b) that activities will be commensurate with the duties and responsibilities of the participants in the process of protection of human subjects of research and compatible with Department of Health and Human Services' (DHHS) Office of Human Research Protections (OHRP) policies; and

(c) that research ethics training will be incorporated into the continuing education program at all DOD Component activities that conduct research involving human subjects.

(2) 32 CFR 219.107 directs that IRBs must have an understanding of "applicable law, and standards of professional conduct and practice."

(3) AR 70-25, paragraph 2.9a(2) requires that IRB members have knowledge of current moral, ethical, and legal standards.

3-2. Applicability and Training Requirements

a. These human subjects protection education requirements apply to:

(1) Investigators, key research personnel (for the purposes of this policy, key research personnel include persons listed on the protocol who have direct contact with subjects or their records/data/identifiable specimens), and medical monitors involved in human research projects where the HQ USAMRMC IRB serves as the IRB of record;

(2) HQ USAMRMC IRB members and Administrator; and

(3) USAMRMC IRB Office and ORP Human Subjects Protection Scientists (HSPSSs) who conduct pre-reviews and life cycle management of protocols for which the HQ USAMRMC IRB serves as the IRB of record.

b. Specific Training Requirements.

(1) Investigators, key research personnel, and medical monitors.

(a) Investigators, key research personnel, and medical monitors conducting Biomedical research: completion of sixteen (16) modules of the University of Miami Collaborative Institutional Training Initiative (CITI), web-based, self-contained course for biomedical focused research at <http://www.citiprogram.org/>, meets the initial USAMRMC education requirements (see Appendix C). Continuing education in human subjects protection must be completed every three (3) years by either an additional six (6) CITI refresher modules of choice or six (6) hours of equivalent continuing education training.

(b) Investigators, key research personnel, and medical monitors conducting Social-Behavioral research: Completion of thirteen (13) modules of the CITI, web-based, self-contained course for social behavioral focused research at <http://www.citiprogram.org/>, meets the initial USAMRMC education requirements (see Appendix C). Continuing education in human subjects protection must be completed every three (3) years by either an additional six (6) CITI refresher modules of choice or six (6) hours of equivalent continuing education training.

(c) Investigators, key research personnel, and medical monitors conducting research with Vulnerable Populations. In addition to the requirements listed in 6.a or 6.b for biomedical or social-behavioral research, if the research involves pregnant women, children, prisoners, workers, students or employees, personnel must complete related CITI modules (see Appendix C).

(d) Investigators, key research personnel, and medical monitors involved in research at International Sites. In addition to the requirements listed in 6.a or 6.b for biomedical or social-behavioral research, if the research involves an international site, personnel must complete the "International Research - SBR" CITI module.

(e) Investigators, key research personnel, and medical monitors involved in research within the Veteran's Administration (VA): In addition to the requirements listed in 6.a or 6.b for biomedical or social-behavioral research, if the research involves working with the VA, personnel must complete the "Human Subjects Research at the VA" CITI module.

(2) HQ USAMRMC IRB members, Chair, Vice Chair, and Administrator.

(a) HQ USAMRMC IRB members, Chair, Vice Chair, and Administrator are responsible for the completion of twenty-seven (27) modules of the University of Miami Collaborative Institutional Training Initiative (CITI), web-based, self-contained course at <http://www.citiprogram.org/> (see Appendix C) or for providing documentation of previous completion of the course within the past three years. Continuing education in human subjects protection must be completed every three (3) years by either an additional six (6) CITI refresher modules of choice or six (6) hours of equivalent continuing education training.

(b) In addition to completion of CITI training, HQ USAMRMC IRB members must complete initial and ongoing training in the IRB's responsibility for implementation of the provisions of the Privacy Rule of the Health Insurance Portability and Accountability Act (HIPAA).

(c) After completing introductory training, each prospective HQ USAMRMC IRB member must attend at least two meetings as an observer, having reviewed read-ahead materials, before becoming a voting member.

(d) The HQ USAMRMC IRB Chair and/or Vice Chair and IRB Administrator will meet individually with each new member prior to their assumption of IRB duties to:

(1) Introduce training materials, self-study requirements, and expectations;

(2) Discuss the roles of voting members, including the prospective member's own expertise and the overall responsibilities of the HQ USAMRMC IRB, alternates, and primary reviewers;

(3) Encourage members and alternates to participate actively in HQ USAMRMC IRB meetings;

(4) Orient new members and alternates about attendance, protocol review, discussion, and presentation responsibilities and schedules.

(e) At each HQ USAMRMC IRB meeting a relevant journal or article will be included in the read-ahead materials provided to members in advance of the Board meeting. The Chair will discuss these reading materials during the opening of each IRB meeting. Additionally, as appropriate, the following may also be offered:

(1) Brief presentations by invited local or visiting experts on scientific or administrative IRB issues.

(2) Brief presentations of highlights and trends from meetings, conferences, or site visits by the HQ USAMRMC IRB members or the ORP staff.

(f) Attendance at an annual meeting of the Public Responsibility in Medicine and Research (PRIM&R) within two years of HQ USAMRMC IRB membership is recommended.

(g) Periodic off-site conferences (1 - 2 days) will be held for primary and alternate members as well as designated IRB Office staff on topics relevant to IRB issues.

(3) Human Subjects Protection Scientists (HSPSs) who conduct pre-reviews and life cycle management of protocols for which the HQ USAMRMC IRB serves as the IRB of record.

(a) HSPSs are responsible for the completion of twenty-six (26) modules of the University of Miami CITI, web-based, self-contained course at <http://www.citiprogram.org/> (see Appendix C) or for providing documentation of previous completion of the course within the past three years.

(b) Continuing education in human subjects protection must be completed every three (3) years by either an additional six (6) CITI refresher modules of choice or six (6) hours of equivalent continuing education training.

(c) In addition to the above CITI training, new HSPSs will complete the following educational supplements:

(1) Read the publication, "Protecting Study Volunteers in Research," by Dr. Cynthia Dunn and Dr. Gary Chadwick, and complete and pass the written test.

(2) Review Public Responsibility in Medicine and Research (PRIM&R) Investigator 101, a self-paced course via CD ROM, and complete and pass the exam.

(3) Attend one or more HQ USAMRMC IRB meetings as an observer.

(d) Attendance at the PRIM&R conference every two years is recommended.

c. In addition to the required training specified above, individuals conducting, reviewing, and/or approving human subjects research submitted to the HQ USAMRMC IRB as the IRB of record are responsible for acting in accordance with specific laws, regulations, policies, procedures, and guidance applicable to the HQ USAMRMC IRB. Relevant documents will be provided to new IRB members and HSPSs during their orientation, and familiarity with the requirements will be achieved by self-study of these materials.

3-3. Training Record Maintenance Responsibilities

a. HQ USAMRMC IRB Administrator. The Administrator will ensure that human subjects research ethics training records are maintained for all personnel subject to this policy. Records will be maintained and tracked as follows for all required education and training:

(1) For investigators/key research personnel/medical monitors: Human subjects research ethics education and training certificates will be maintained in the IRB protocol master files. See section 3-3.b below for additional information.

(2) For HQ USAMRMC IRB members, Chair, Vice Chair, and Administrator: All human subjects research ethics training will be entered in the ORP Information Management System (IMS) training module by IRB Office staff upon completion. Oracle Discoverer reports will be generated monthly to track expiration of CITI training. The HQ USAMRMC IRB members will be notified by email of the need to complete refresher training three (3) months in advance of expiration of training.

(3) For ORP IRB Office HSPSs: All human subjects research ethics training will be entered in the ORP IMS training module by IRB Office staff upon completion. Oracle Discoverer reports will be generated monthly to track expiration of CITI training. HSPSs will be notified by email of the need to complete refresher training three (3) months in advance of expiration of training.

b. HSPS. HSPSs conducting pre-reviews and life cycle management of protocols are responsible for assessing compliance with this policy for the investigators/key research personnel/medical monitors during initial protocol review as part of the pre-review process and at the time of continuing review. HSPSs will communicate with investigators to provide

information regarding training requirements and collect training certificates for research personnel. These certificates will be maintained in the protocol's IRB master file. At the time of continuing review, the HSPS will reassess the status of all study personnel's human subjects research ethics training and will coordinate with the Principal Investigator as needed to obtain documentation of continuing training.

c. Individual Responsibility. All individuals subject to this policy are responsible for keeping accurate records of their initial and continuing training.

Chapter 4. HQ USAMRMC IRB Membership, Appointment and Quorum Requirements

This chapter briefly describes the primary and alternate membership, appointment and meeting quorum requirements that are detailed in the March 2010 HQ USAMRMC IRB Charter.

4-1. Membership

a. Composition. The HQ USAMRMC IRB must include members able to ascertain the acceptability of proposed research in terms of the regulatory requirements governing human subjects protection. Composition of the membership is based upon ongoing analysis of the broad categories of research reviewed by the IRB, and members will possess knowledge, experience, scientific or scholarly expertise in the types of protocols most frequently reviewed by the Board.

(1) Qualifications. The HQ USAMRMC IRB members will be sufficiently qualified and have the experience, expertise, and community sensitivity needed to adequately review research activities presented to the HQ USAMRMC IRB.

(2) Membership Diversity. The HQ USAMRMC IRB is constituted IAW the requirements of 32 CFR 219.107. The IRB is comprised of a minimum of seven voting members, of varying backgrounds with regard to service, race, gender, culture, and profession. As such, it does not consist entirely of men or of women, or entirely of members of one profession. The IRB includes at least one member whose primary concerns are in scientific areas, at least one member whose primary concerns are in nonscientific areas, and at least one primary member who is not otherwise affiliated with the federal government.

(3) Vulnerable Subjects. When the HQ USAMRMC IRB reviews research that involves a vulnerable category of subjects, such as children, prisoners, pregnant women, handicapped, or mentally disabled persons, individuals with acute or severe physical or mental illness, or those who are economically or educationally disadvantaged, it includes one or more individuals who specifically represent concerns of these subject populations.

(4) Consultants. The HQ USAMRMC IRB uses its discretion to invite individuals with competence in special areas to assist in the review of complex issues that require expertise beyond or in addition to that available on the Board. These invited subject matter expert individuals may not vote with the IRB.

(5) Requirement for Federal Employment. In accordance with DODD 3216.02, HQ USAMRMC IRB members will be military or civilian employees of the federal government; individuals covered under the Intergovernmental Personnel Act (IPA) or intermittent consultants consistent with the requirements established by 5 USC 3109. Members who are not federal employees are engaged as IPAs or intermittent consultants IAW 5 USC 3109 for the purposes of membership on the HQ USAMRMC IRB.

(6) Review of IND for FHP)Protocols. DOD Instruction (DODI) 6200.02 directs that the HQ USAMRMC IRB serve as IRB for the review of any contingency IND protocol for FHP. The HQ USAMRMC IRB membership also meets the specific requirements IAW 21 CFR 50.23(d) for review of FHP IND protocols for which the Secretary of Defense requests a waiver of prior informed consent from the President of the United States (see Chapter 14). There must be at

least three non-affiliated members (primary or alternate) who are not employees of the federal government (other than for purposes of membership on the IRB) to meet this requirement.

4-2. Membership Appointment and Designation of Members to Perform Additional Duties

a. The HQ USAMRMC IRB Chair and/or Director, Human Research Protection Office (HRPO) recommend potential members to the CG, USAMRMC, who serves as the Institutional Official. The CG, USAMRMC appoints HQ USAMRMC IRB members for terms of no more than four years, and has the discretion to re-appoint members for additional four-year terms.

b. In accordance with 32 CFR 219.110.(b)(2), one or more experienced HQ USAMRMC IRB members can be designated to perform expedited reviews and approvals. Members who have attended a minimum of 10 HQ USAMRMC IRB meetings at which they served as a primary reviewer for protocol actions across the spectrum of life cycle issues (i.e., initial reviews, continuing reviews, amendments, etc.) may be considered for this designation. Designations are made in writing by the HQ USAMRMC IRB Chair.

c. An Acting Chair can be drawn from among the experienced HQ USAMRMC IRB members to provide leadership during convened IRB meetings. An Acting Chair may serve for a single meeting when the Chair or Vice Chair is unavailable. Members who have attended a minimum of 10 HQ USAMRMC IRB meetings at which they served as a primary reviewer for protocol actions across the spectrum of life cycle issues (i.e., initial reviews, continuing reviews, amendments, etc.) may be considered for this designation. Designations are made in writing by the HQ USAMRMC IRB Chair. Additionally, an Acting Chair may be appointed by the CG, USAMRMC to serve as an interim Chair for a finite period of time while a permanent Chair is identified.

4-3. Quorum

a. Presence of a majority (more than half) of the appointed primary members constitutes the quorum at a convened meeting. Board recommendations shall be made at a convened meeting that meets quorum requirements. Of the members required to be present for quorum to be met, at least two must be physicians, one member must be an individual whose primary concerns are in nonscientific areas and one member must be unaffiliated with the federal government.

(1) To count towards the quorum, attendance must be in person, by video teleconference, or by telephone. There is no proxy voting. Each participating IRB member must receive and review a complete read-ahead packet prior to the meeting and is encouraged to participate actively and equally in the discussion of all protocols.

(2) Actions on recommendations by the Board will be based on a simple majority vote of members present (32 CFR 219.108).

(3) Should the quorum fail during a meeting, no further review may continue and no votes may be taken until the quorum is fully restored.

b. A military or civilian attorney within the USAMRMC Office of the Staff Judge Advocate (SJA) must render an opinion before a formal HQ USAMRMC IRB vote can be taken. This opinion may be submitted in writing if the legal representative is unable to attend. When present at a convened meeting, the legal representative IRB member counts as a voting member.

c. In addition, IAW 21 CFR 50.23(d), if feasible, a majority of the nonaffiliated members will be present for the review of any contingency IND for FHP protocol for which the Secretary of Defense requests a waiver of prior informed consent from the President of the United States.

Chapter 5. Conflict of Interest

This chapter describes the requirement for management of financial and other conflicts of interest for (1) HQ USAMRMC IRB members and ORP IRB Office staff members and (2) investigators and research staff members.

5-1. Background

a. Conflict of interest (COI). A COI arises when an individual is or may be in a position to influence research or other decisions in ways that could lead to any form of personal gain for the individual or his/her immediate family, or give improper advantage to others. A real or perceived COI may take various forms that include, but are not limited to when an individual:

- (1) Engages in an action or decision that compromises the integrity of research;
- (2) Has a personal relationship that may cause bias or create the appearance of bias;
- (3) Holds a leadership position in a business entity or organization (e.g., service as an officer, member of the board of directors, or in any other position of trust, confidence, and responsibility whether or not the individual receives compensation for such service) that is engaged in the research.

b. Types of COI.

(1) Financial COI. A person has a significant financial interest with respect to a protocol when he/she and or his/her immediate family receives in aggregate any of the following over a 12-month period: (a) Compensation of a value that could be affected by the study outcome; (b) A proprietary interest in the tested product included but not limited to, a patent, trademark, copyright or licensing agreement, or the right to receive royalties from product commercialization; (c) Any equity interest in the sponsor or product of a value that cannot be readily determined through reference to public prices (e.g., ownership interest or stock options); (d) Any equity interest in the sponsor or product that exceeds \$10,000 or 5% ownership interest; (e) Significant payments or other sorts with a cumulative value of \$10,000 made directly by the sponsor as an unrestricted research or educational grant, equipment, consultation, or honoraria, or other payment.

Significant financial interest does not include: (a) salary or other remuneration from the USAMRMC; (b) income from seminars, lectures, or other teaching engagements sponsored by public or non-profit entities; (c) income from service on advisory committees or review panels for public or non-profit entities; (d) holdings in mutual funds or pension accounts over which the individual or his/her immediate family (i.e., spouse, domestic partner, and/or dependent child) does not exercise control; (e) an equity interest that when aggregated for the individual and their immediate family, meets both of the following tests: does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, or does not represent more than a five percent (5%) ownership interest, regardless of value, in any single entity; or (f) salary, royalties or other payments that when aggregated for the individual or their immediate family over the next 12 months are not expected to exceed \$10,000.

(2) Other Conflicts of Interest. Not all COIs are financial. Other examples of COI that could apply to HQ USAMRMC IRB members/staff and/or investigators/research staff include:

- (a) Command influence.
- (b) Employer/employee relationships.
- (c) Potential for personal reward.

5-2. Conflict of Interest and HQ USAMRMC IRB Members/Staff

a. Prohibition of COI. It is essential that the members of the HQ USAMRMC IRB, subject matter expert consultants, and ORP IRB Office support staff (e.g., IRB Director/Administrator, HSPSs) remain free from any COI between their personal interests and/or their official capacity outside the IRB, and their HQ USAMRMC IRB responsibilities in regard to the protocols they review. It is the policy of the HQ USAMRMC IRB that IRB members, subject matter expert consultants and ORP IRB Office support staff with a potential or actual COI may not participate in any portion of the review of research activities, except to provide information requested by the IRB, and must not be present during the IRB's deliberative discussion and vote on the affected research. All potential and actual COI of an IRB member, subject matter expert consultant or ORP IRB Office support staff member must be declared before review of any research under HQ USAMRMC IRB jurisdiction.

b. Examples of Prohibited Conflicts. These include, but are not limited to:

(1) Potential for Personal or Financial Gain. A Board member may not deliberate or vote on a protocol in which the member or a member of his/her immediate family is a corporate officer, stockholder, consultant or employee, regardless whether his/her vote would be in favor or against the protocol.

(2) Potential for Personal Reward. A Board member who is affiliated with a protocol in the capacity of Principal Investigator, associate investigator, co-investigator, commander, Sponsor's Representative (i.e., the person who signs FDA Form 1571), or person who is responsible for securing funds or for otherwise promoting the research (e.g., the product manager for the product being used in the study) may not deliberate or vote on the protocol, regardless of whether his or her vote would be in favor of or against the protocol.

(3) Command Influence. The Command's research and development mission (for example, an operational need for the results of the research) should not override or obscure IRB methods. Urgent or compelling need may enter the HQ USAMRMC IRB members' risk-benefit analysis, but it must not supersede deliberate analysis of the protocol. The Board must always operate and be seen as operating as a reasonable, deliberative, body, whose objective is to protect the safety and welfare of the research subject. It is incumbent upon each IRB member, through the Board's deliberative processes, to find satisfactory answers to his or her concerns regarding the moral, ethical, and legal issues of each protocol before voting according to his or her conscience. Therefore, a HQ USAMRMC IRB member may not deliberate or vote on a protocol if the member feels that he/she has been subject to undue command influence to approve the protocol.

c. Procedure. At the beginning of each HQ USAMRMC IRB meeting, the Chair will ask if any IRB members have COIs regarding any of the protocols to be discussed. Members must disclose all conflicts and recuse themselves from deliberating or voting on the protocol(s) with

which they have a COI, and will leave the meeting room during the Board's deliberations and vote.

5-3. Conflict of Interest and Investigators/Research Staff

a. Rationale for Prohibition of COI. COIs may reduce the objectivity of research by affecting the design, conduct, or reporting of research, or the analysis and interpretation of data (see 42 CFR 50.601). If research is designed or conducted improperly, its value is limited. It is not ethical to involve human subjects in research that is of no, or very limited, value. COIs may also affect subject safety. For example, an investigator with a COI may, even if unwittingly, color the consent discussion by minimizing the risks or overstating the benefits, or dismissing the value of alternative treatments. A COI may also affect an investigator's willingness to report adverse reactions possibly related to the study article. Investigators with a COI may also improperly include or exclude subjects (OHRP Guidance).

b. Investigator Disclosure Requirement. Investigators must disclose to the HQ USAMRMC IRB any significant financial interest with a research sponsor, and any other significant financial interest that may reasonably appear to affect or be affected by the research.

(1) Though there is no required format for the disclosure, the disclosure must:

(a) be in writing;

(b) include the investigator's name, title, and organization, the name of the research protocol, and a list of all sponsors of the protocol;

(c) list all significant financial interests with a research sponsor, and all other significant financial interests that may reasonably appear to affect or be affected by the research. The list must include the name of the organization in which the investigator has an interest, the nature of the interest (e.g., salary, equity, intellectual property rights) and a detailed description of the interest including the approximate dollar amount.

(d) list steps taken, if any, to minimize potential for harm to subject safety or research objectivity resulting from any of the disclosed interests;

(e) if there are no interests to disclose, include the statement "I certify that I have no significant financial interests with a research sponsor, or that may otherwise reasonably appear to affect or be affected by the research."

(f) be dated and signed by the investigator;

(g) be submitted along with the protocol for review by the IRB.

(2) The disclosure must be updated if the investigator acquires new significant financial interests with a sponsor, or new significant financial interests that may otherwise reasonably appear to affect or be affected by the research, during the conduct of the research, the investigator's analysis of the research data, or the investigator's reporting of the research results (see 42 CFR 50.604).

b. Eliminating, Managing or Reducing COIs. If the HQ USAMRMC IRB determines that any of the disclosed interests are COIs, the IRB will determine how to satisfactorily resolve the COIs.

(1) COIs should be eliminated, if possible. Examples of possible actions to eliminate a COI include, but are not limited to divestiture of the interest, severance of the relationship that creates the interest, or disqualification of the investigator from participating in the research.

(2) If an investigator cannot eliminate a COI, the investigator should manage or reduce the scope of the COI. Examples of possible actions to manage or reduce a COI include but are not limited to:

(a) modifications to the protocol, including the research plan;

(b) objective, third-party oversight of the research or consent process;

(c) having a non-biased third party obtain consent, especially when potential COIs could influence the tone or presentation of information during the consent process;

(d) modification of consent form;

(e) disqualification from participation in a portion of the research that could be affected (see 42 CFR 50.605). For example, disqualification from design of the research, AE reporting, or analysis of the data.

(3) The HQ USAMRMC IRB will not approve research until it is satisfied that COIs have been or will be eliminated, managed, or reduced.

c. Disclosure to Subjects in the Consent Form. If the HQ USAMRMC IRB believes that a COI cannot be eliminated, and that the COI could be considered material to a potential subject's decision-making process (i.e., when subject is assessing risks and benefits or the merits of the research itself), the investigator must inform the subject in the consent process and form of the existence and nature of the COI. The consent process and form should also document how the COI is being managed, and what additional protections have been put in place.

(1) Subjects must be informed in easily understandable language.

(2) Investigators should disclose to subjects only COIs, not other financial interests.

(3) The dollar amount of the COI should not be disclosed to the subject.

d. Maintenance of Financial Disclosure Statements. The HQ USAMRMC IRB will maintain records of financial disclosures and actions taken with respect to each COI for at least one year from the date of completion of research (see 42 CFR 50.604).

e. Confidentiality of Financial Disclosure Statements. To the extent permitted by law, the HQ USAMRMC IRB will maintain the confidentiality of all records of financial disclosure (see 42 CFR 50.606). For example, if any such records are sought under the Freedom of Information Act (FOIA), the custodian of the records will seek legal counsel and request that the government assert all applicable exemptions to disclosure under FOIA. The HQ USAMRMC IRB will take

steps to ensure that financial disclosure statements are only accessible to personnel with a need to review those statements.

f. Failure to Manage or Reduce COIs. The HQ USAMRMC IRB may suspend research if it believes that an existing COI is not being reduced or managed in accordance with the IRB's directions, or a new COI is deemed to threaten the safety of the subject or the objectivity of the research, or upon discovery that the investigator failed to disclose a COI.

Chapter 6. Human Subjects Research Review

This chapter describes the requirements and procedures for initial review of research by the HQ USAMRMC IRB.

6-1. Scientific Peer Review of Research

Scientific peer review ensures that research is scientifically sound in its design and methods, and the proposed research is worthy of performance. The HQ USAMRMC IRB requires that documentation of prior criteria-based scientific review of a proposal / protocol accompany its submission for IRB review.

Documentation should demonstrate that the scientific review assessed issues such as: the significance of the research (e.g., whether the study address a problem of scientific and/or practical importance, how scientific knowledge be advanced, the effect of the study on the concepts or methods that drive the particular field of research, important practical benefits to military and/or civilian communities that may derive from successfully achieving the study's stated aims); the approach (e.g., whether the conceptual framework, design, methods and analyses are adequately developed, well-integrated and appropriate to the aims of the study, whether the investigator acknowledges potential problem areas and consider alternative tactics); the investigators' qualifications and experience; and the scientific environment (i.e., whether the scientific environment in which the study will be done will contribute to the probability of success).

6-2. Other Reviews

a. Reviews by Other Organizations/Committees. At times, research may be subject to regulatory review and approval of other organizations or committees such as the Food and Drug Administration (FDA), Institutional Biosafety Committees, Radioactive Drug Research Committees, Safety Committees, Recombinant DNA Advisory Committee, etc. Research managers, Sponsors and Principal Investigators are responsible for ensuring that required reviews take place. As appropriate, the HQ USAMRMC IRB may request documentation that required committee reviews and approvals are in place prior to review and approval of a protocol.

b. Letter of Support. A letter of support from the Commander of military facilities or units in which subject recruitment will occur or the study will be conducted must be obtained before approval. Additionally, volunteers may be required to seek written permission from their supervisor prior to participation in research studies.

c. Survey Research. Attitude and opinion surveys of Army personnel conducted in two or more major commands (Army Commands, Army Service Component Commands, or Direct Reporting Units) must be approved by the Army Research Institute prior to administration, IAW AR 600-46 (Attitude and Opinion Survey Program). Attitude and opinion surveys of military members conducted in two or more DOD Components (Services) must be approved by the Defense Manpower Data Center, IAW DODI 1100.13 (Surveys of DOD Personnel). This approval must be in place prior to final IRB approval.

d. Other components such as Navy and Air Force have specific requirements for human research. There may be additional service-specific approvals required when research is conducted in other component's facilities or with their personnel.

6-3. Pre-review and Determination of Review Pathway by the ORP IRB Office

Protocols submitted to the ORP IRB Office for review by the HQ USAMRMC IRB are forwarded to the IRB Administrator for initial assessment of whether the activity meets the definition of human subjects research based on the definitions in 32 CFR 219.102, assessment of the study's probable risk level, and assignment of the protocol to a HSPS. HSPSs carry out checklist-based preliminary reviews of protocols and associated materials. The HSPSs examine the materials in detail, and assess the basis for an exemption determination by consulting the exemption criteria at 32 CFR 219.101.b; or the basis for expedited review procedure by consulting the "Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure" from the 63 Federal Register (FR) 60364-60367, November 9, 1998. Subsequently, the Chair, Vice Chair, HQ USAMRMC IRB member designee or the IRB Administrator reviews the protocol documents and provides the final determination regarding whether the activity is human subjects research, and whether the project qualifies for expedited review or requires full Board review.

6-4. Determinations of 'Not Research,' Research Not Involving 'Human Subjects' or Exempt Human Subjects Research

a. General Information. Prior to implementation, investigators who propose to conduct projects that may involve human subjects in research must submit project descriptions to the ORP IRB Office for a determination of whether the effort is "research" as defined in 32 CFR 219.102. The project is further reviewed to determine if the research involves "human subjects." If the study is determined to be "research" but does not involve "human subjects" as defined in 32 CFR 219.102, the project is not subject to the provisions of 32 CFR 219. Finally, if the project constitutes research involving human subjects, it is then evaluated to determine if it meets a criterion at 32 CFR 219.101(b) that would classify it as human subjects research exempt from the human subjects protection regulations at 32 CFR 219.

b. Authority for Making Determinations.

(1) Investigators do not have the authority to make independent determinations for projects that may involve human subjects research. The institution engaged in research must address who will make these determinations in their approved HRPP. If no provisions have been made within the HRPP for an alternate pathway, Investigators must submit sufficient information to the ORP IRB Office in order for a determination to be made.

(2) The assessment of whether an activity is not research, is research not involving human subjects or is exempt human subjects research may be made by ORP IRB Office staff members designated to make these determinations. They may also be made by the HQ USAMRMC IRB Chair, Vice Chair, or designated IRB member.

c. Revisions to Projects. Changes in projects determined to be "not research," research not involving "human subjects" or exempt human subjects research that could affect their determination status must be reviewed by the ORP IRB Office prior to implementation.

6-5. "Not Research" and Research Not Involving "Human Subjects"

a. A designated ORP IRB Office staff member determines whether a project involves human subject research by considering if the activity either:

- (1) Meets the regulatory definitions of “research” that involves “human subjects;” or
- (2) Meets the regulatory definition of “clinical investigation.”

b. Investigators will be notified, in writing, if projects are determined to not involve human subjects research, and are therefore not subject to the regulatory requirements in 32 CFR 219. Such activities may be found to be:

(1) Not Research. Activities are not research as defined in 32 CFR 219.102.d if they do not involve a systematic approach involving a predetermined method for studying a specific topic, answering a specific question, testing a specific hypothesis, or developing theory and the activity is not designed to develop or contribute to generalizable knowledge. Examples of activities that would not normally be considered research include, but are not limited to:

(a) Training activities (e.g., human subjects being trained to perform a certain technique or therapy such as art therapy, psychoanalysis, oral history techniques).

(b) Classroom exercises involving human participants or human participant data where the objective of the activity is to teach proficiency in performing certain tasks or using specific tools or methods.

(c) Quality Assurance (QA) activities designed to improve the quality or performance of a department or program where it is not the intention to share resultant data beyond the immediate community conducting the activity.

(2) Research Not Involving Human Subjects. Activities do not involve human subjects as defined in 32 CFR 219.102.f if they do not involve the process of (a) obtaining specimens or data about the individual through intervention or interaction with individual subjects or (b) identifiable private information. Examples of activities that would be considered research not involving human subjects include, but are not limited to:

(a) Research with anonymized data or specimens, i.e., no links remain that could allow identification of the individual from whom the data or specimens were obtained.

(b) Research with coded specimens or data where the Principal Investigator will not have access to identifiers.

(c) Developmental and operational testing of new equipment in which no data about the individual operator(s) is/are collected.

(3) Cadaver Research. Research using cadavers or cadaveric materials is not considered human subjects research as the definition of human subject specifies that a “human subject means a *living* individual . . .” (32 CFR 219.102.f).

6-6. Exempt Human Subjects Research

a. Certain research involving human subjects is exempt from the regulatory requirements of 32 CFR 219. The categories of research that are exempt from the federal regulations are found in 32 CFR 219.101(b). Department or agency heads may make the final determination of whether a given research protocol is exempt (32 CFR 219.101(c)). Note that exempt research

activities are subject to the same human subjects protections and ethical standards as outlined in The Belmont Report.

b. A designated ORP IRB Office staff member determines whether a project involves exempt human subject research by considering whether the research meets one or more of the exemption criteria under 32 CFR 219.101(b).

c. Investigators will be notified, in writing, of the applicable exemption category(ies) under which the research activity was determined to be exempt from the regulatory requirements at 32 CFR 219 if all proposed research activities in a project involve one or more of the following categories. NOTE: These categories do not apply to research involving prisoners; categories 2 and 3 may not apply to research with children; and categories 1-5 do not apply to FDA-regulated research.

(1) Exemption # 1: [32 CFR 219.101(b)(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) Exemption # 2: [32 CFR 219.101(b)(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 indirectly 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) Exemption # 3: [32 CFR 219.101(b)(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 (as described above) 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) Exemption # 4: [32 CFR 219.101(b)(4)] Research involving the collection or study of existing data, documents, records, and pathological or diagnostic specimens if these sources are publicly available, or if the information is recorded in such a way that volunteers cannot be identified directly or through identifiers linked to the volunteer.

(5) Exemption # 5: [32 CFR 219.101(b)(5)] Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

- (a) Public benefit or service programs or
- (b) Procedures for obtaining benefits or services under those programs or
- (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) Exemption # 6: [32 CFR 219.101(b)(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 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.

6-7. "Expedited" Review

a. An expedited review procedure consists of the review of human subjects research by the HQ USAMRMC IRB Chair, Vice Chair, or by an experienced reviewer designated by the Chair or Vice Chair from among the IRB members IAW the requirements set forth in 32 CFR 219.110. In conducting expedited review the reviewer may exercise all of the authorities of the IRB except that s/he may not disapprove the research. A research activity may be disapproved only after review by the convened HQ USAMRMC IRB in accordance with the procedure at 32 CFR 219.108(b).

b. The IRB may use the expedited review procedure to review either or both of the following:

(1) Research appearing on the Federal Register list of expedited categories and found by the reviewer(s) to involve *no more than minimal risk*.

(2) Minor changes in previously approved research during the period of one year or less for which approval is authorized (32 CFR 219.110; 21 CFR 56.110). Minor changes in approved research cover the following situations:

(a) Studies may be approved for implementation following the HQ USAMRMC IRB Chair's, Vice Chair's or designated IRB member's administrative review of responses submitted to comply with specific stipulations of the IRB (i.e., protocols approved pending receipt of specific modifications or additional documents).

(b) Administrative amendments, minor modifications to an already approved protocol or consent form, additional versions of approved consent forms, recruitment posters or advertisements, and changes in study staff if the HQ USAMRMC IRB Chair, Vice Chair or designated IRB member has found that the change(s) would have no significant impact on the conduct of the study or detriment to the previously approved plan for protection of human subjects.

c. The requirements for informed consent (or its waiver or alteration) and special considerations for vulnerable populations apply to protocols eligible for expedited review (see Chapters 8 and 9).

d. All protocols initially reviewed and approved by expedited procedure are reviewed for continuation by the HQ USAMRMC IRB Chair, Vice Chair, or designated IRB reviewer at least once per year. The date of initial conditional or full approval determines the date by which the first continuing review must occur.

e. Investigators will be notified, in writing, of the applicable expedited review category(ies) under which the research activity was reviewed and approved.

f. All HQ USAMRMC IRB members and the CG, USAMRMC will be advised of protocol actions that have been approved under expedited review procedures by inclusion of a list of such approvals in the read-ahead materials for IRB meetings and/or by delivery of the list via electronic mail.

6-8. Nine Categories of Research Approvable by Expedited Review

In conducting an expedited protocol review, the HQ USAMRMC IRB Chair, Vice Chair, or designated IRB reviewer will consider criteria for approval identified in 32 CFR 219.111 and other applicable laws, regulations, or policies (see Chapters 7, 8, 9, 10). Initial or continuing review of research may be conducted by expedited procedure provided all research activities involve procedures listed in, or consistent with, one or more of the following categories quoted from the Federal Register (63 FR 60364-60367; November 9, 1998):

(1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.

(a) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

(b) Research on medical devices for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.

(2) Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(a) from healthy, nonpregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or

(b) from other adults and children², considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.

(3) Prospective collection of biological specimens for research purposes by noninvasive means.

Examples: (a) hair and nail clippings in a nondisfiguring manner; (b) deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction; (c) permanent teeth if routine patient care indicates a need for extraction; (d) excreta and external secretions (including sweat); (e) uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques; (i) mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings; (j) sputum collected after saline mist nebulization.

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

Examples: (a) physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy; (b) weighing or testing sensory acuity; (c) magnetic resonance imaging; (d) electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography; (e) moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

(5) Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as 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 (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

(8) Continuing review of research previously approved by the convened IRB as follows:

(a) where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; or

(b) where no subjects have been enrolled and no additional risks have been identified; or

(c) where the remaining research activities are limited to data analysis.

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

6-9. Convened IRB Meetings

All protocols not eligible for expedited review and approval are reviewed by the convened HQ USAMRMC IRB.

a. Distribution of Protocol-Related Documents to IRB Members.

(1) Approximately two weeks prior to scheduled meetings, HQ USAMRMC IRB members are contacted by email/phone by the ORP IRB Office staff to determine their availability for the meeting. At least five calendar days prior to an IRB meeting, read-ahead packets of materials to be reviewed at that meeting are delivered to each attending IRB member. Board members' receipt of their read-ahead packets is verified by email or delivery service confirmation. All members of the HQ USAMRMC IRB are provided the same documentation in their read-ahead packets and all are expected to actively participate in the review and discussion of the protocol.

(2) The read-ahead packets contain the protocols or other actions for review, an agenda with primary reviewer member assignments, minutes from previous IRB meetings (when available), a list of protocol actions approved by an expedited procedure, educational materials, and other administrative items as necessary.

(3) Components of the protocol read-ahead packet:

(a) A review document summarizing the protocol, the risks and benefits to the subjects, the regulatory issues involved, and the assigned HSPS's recommendations to be considered by the IRB;

(b) Checklists used in the pre-review of the protocol;

(c) Expert consultant report and recommendations as necessary;

(d) Consent form(s) and/or assent forms (when applicable);

(e) Copy of the full protocol;

(f) Documentation of scientific review;

(g) Curriculum Vitae (CV) of the Principal Investigator and the medical monitor;

(h) Data collection instruments/case report forms;

(i) Advertisements and other recruitment materials;

(j) Product and/or device information as applicable;

(k) Additional correspondence, as needed;

(l) Other regulatory documents as appropriate.

(4) For review of FDA-regulated protocols involving Investigational products and/or devices the read-ahead packet will also contain the following additional items:

(a) Investigator's Brochure or Device Manual;

(b) Form FDA 1572.

b. Use of a Primary Reviewer System.

(1) In order to promote a thorough review of protocols, the HQ USAMRMC IRB uses a primary reviewer system in which studies are assigned to one or more voting members for an in-depth review of all materials in the read-ahead packet and presentation of the protocol at the meeting.

(2) One or more IRB members with experience/expertise in the subject matter of the protocol are assigned as primary reviewers. When appropriate, at least one of the primary reviewers is a physician member.

(3) Primary reviewers are provided a review template to aid in their assessment and presentation of the protocol. Review summaries completed by a primary reviewer before the meeting are circulated to all attending Board members, and are included in the enclosures to the minutes.

c. Pre-Meeting Questions and Responses.

(1) The primary reviewer(s) and all IRB members may submit questions for the Principal Investigator to the IRB Office staff before the scheduled IRB meeting in sufficient time for the Principal Investigator to respond to the questions in writing before the meeting. The ORP IRB Office staff sends the Principal Investigator's responses to the Board members scheduled to attend the meeting. (Written responses received the day of the meeting will only be forwarded to members at the direction of the IRB Chair or Administrator to alleviate confusion among Board members who do not receive the Principal Investigator's response in time for the meeting.)

(2) Pre-meeting questions for which responses were circulated to attending IRB members are included in the enclosures to the minutes.

d. Meeting Conduct.

(1) Meeting Leadership.

(a) HQ USAMRMC IRB Chair. The Chair presides over convened meetings and serves as a voting member.

(b) HQ USAMRMC IRB Vice Chair. The Vice Chair serves as a voting member and presides over convened meetings in the absence of the Chair.

(c) In the absence of the Chair or Vice Chair, an Acting Chair can be drawn from among the experienced HQ USAMRMC IRB members to provide leadership during convened IRB meetings (see Chapter 4). An Acting Chair serves as a voting member of the IRB.

(2) Quorum. Unless quorum is attained and maintained throughout the meeting, the HQ USAMRMC IRB may not vote on protocol actions or other issues presented. The IRB Administrator and Chair (or Vice Chair/Acting Chair in the absence of the Chair) will confirm that the HQ USAMRMC IRB's quorum requirements as described in Chapter 4 of this document are met prior to the IRB's review of protocol actions, and will monitor quorum status throughout the meeting, e.g., if any IRB members recuse due to COI or are not present for the review and discussion of a given protocol action.

(3) Conflict of Interest.

(a) As described in Chapter 5 of this document, no HQ USAMRMC IRB member may participate in the IRB's review of any project in which the member may have an actual, apparent, or perceived COI. It is essential that the members of the IRB are perceived as, and in fact are, free from any conflict of interest or the appearance of COI in their daily duties and especially in regard to the protocols they review.

(b) At the start of each meeting of the HQ USAMRMC IRB, the Chair (or Vice Chair/Acting Chair in the absence of the Chair) will solicit information regarding any member having any real, potential, or perceived COI in any of the submissions to be reviewed at that meeting. For each review by the IRB, any member with any type of conflict of interest is required to fully disclose that interest and to completely recuse him/herself from the review of that proposal/protocol. Recusals are recorded by name in the minutes of the meeting, under the discussion of that specific protocol, and the member(s) so recused are considered as absent from the meeting, other than to provide IRB-solicited information, and must leave the meeting room prior to deliberations and vote.

(4) Review and Acceptance of Minutes from Previous HQ USAMRMC IRB Meetings. Minutes from previous HQ USAMRMC IRB meetings are presented to IRB members in the read-ahead packet. The Chair (or Vice Chair/Acting Chair in the absence of the Chair) will ask Board members if they have any additions or corrections to the minutes and accept the minutes as written if no changes are required. Acceptance of previous meeting minutes to include any corrections will be documented in the minutes.

(5) Protocol Review.

(a) The IRB Chair (or Vice Chair/Acting Chair in the absence of the Chair) will initiate the protocol's review, and ask the IRB primary reviewer(s) to provide a summary of the protocol and any issues identified during its review. After general discussion of the protocol, the Principal Investigator (and research team members) will be invited into the meeting room (or connected by teleconference) to answer questions and any succeeding questions and clarifications. The discussion with the Principal Investigator is initiated by the primary reviewer(s).

(b) The Principal Investigator or her/his designee(s) is encouraged to be available to respond to questions during the IRB review of the protocol. The purpose of the Principal Investigator's presence is to provide any additional information and/or clarifications as sought by the reviewers during the review process.

(c) When the Chair (or Vice Chair/Acting Chair in the absence of the Chair) is satisfied that the issues have been reasonably examined, s/he will thank the visitors for assisting in the review process and ask them to leave the room. Any HQ USAMRMC IRB members with a COI will also leave the room. The IRB will consider whether the criteria for approval of human subjects research as described in Chapter 8 of this document are met. After a final discussion of remaining issues, any stipulations and the period of approval will be agreed upon (see Section 6-9.d(6)), a motion will be made and seconded (see Section 6-9.d(7)), and the vote will be recorded. Actions by the Board will be based on a simple majority vote of members present (32 CFR 219.108).

(d) Recommendations from the protocols' pre-review and any items that investigators agreed to modify during the pre-meeting exchange of questions and answers will be included as stipulations unless objections are raised by IRB members during the review.

(6) Determining Which Projects Require Review More Often Than Annually.

(a) 32 CFR 219.103 (4)(ii) requires written procedures that the IRB will follow for determining which projects require review more often than annually. Although the maximum period of IRB approval may extend for one year from the date of initial approval, the HQ USAMRMC IRB may designate an approval period of less than one year. As with annual review, this designation will require a review for continuation prior to the end of the approval period. The following factors may influence the duration of a protocol's approval period:

- 1 Projects that involve significantly high risk to subjects.
- 2 Phase I or II clinical trial protocols for which little documentation of potential risks is available.
- 3 Protocols involving novel procedures involving unknown risks and hazards.
- 4 Protocols involving multiple requests for amendments.
- 5 Protocols with a number of unexpected AEs or other problems.
- 6 Situations involving investigators, institutions, or other contextual factors for which the HQ USAMRMC IRB has reason to be extra cautious.
- 7 Protocols from investigators who are known to have not complied with regulatory requirements in the past.

(b) As an alternative to requiring that continuing review be conducted in less than 12 months, the HQ USAMRMC IRB may require a review after a specific number of subjects have been exposed to the test article or research intervention. The IRB may also specify rules for stopping the study early, require an interim review of study results and adverse effects by the medical monitor, require review of an assessment done by a Data Monitoring Committee (DMC), and/or specify submission of particular data for early review prior to continuation of the study.

(c) When the HQ USAMRMC IRB recommends an approval period shorter than 12 months, the minutes will include the reason(s) for the shorter term of approval and specify any requirements to be fulfilled by the investigator by the end of this period.

(7) The HQ USAMRMC IRB will consider the criteria for approval identified in 32 CFR 219.111 and other applicable laws, regulations, or policies (see Chapters 7, 8, 9, 10). The HQ USAMRMC IRB can make the following recommendations to the CG, USAMRMC.

(a) Approval. The protocol is approved without further revisions.

1 After voting such an action at the end of an initial review, the IRB members discuss and vote on the period (not longer than one year) for which the initial approval is valid. A continuing review report will be required prior to the end of the protocol approval period, and a new review of the study will be conducted (see Chapter 15).

2 Upon receiving the approval signature of CG, USAMRMC on the minutes, the IRB Office will provide the notice of approval to the Principal Investigator, the institution, and other appropriately interested parties.

(b) Conditional Approval. Approval of the protocol is contingent upon the Principal Investigator making specific modifications as stipulated and/or providing additional information.

1 A conditional approval may be given only when the convened IRB stipulates minor modifications or changes requiring simple concurrence by the investigator. These modifications include requirements for specific changes in wording or inclusion of additional but non-critical information to amplify or clarify the current protocol where the exact answer would not change the IRB's approval of the research. Examples include identifying particular study personnel or specifying the type of randomization methodology for a simple study. A conditional approval authorizes the Chair (or designee) to subsequently approve the revised study under an expedited review procedure.

2 The IRB Administrator will forward the IRB's specific and detailed stipulations and recommendations in writing to the Principal Investigator. When appropriate, the assigned HSPS makes provisions for a telephone conversation about the identified issues, in order to help the Principal Investigator understand the required revisions or requested additional information.

3 If the CG, USAMRMC endorses the IRB's conditional approval of a protocol by approving and signing the meeting minutes, the protocol becomes approved upon the Chair's (or designee's) determination that the revisions have been met and/or the information has been provided. The protocol's expiration date is set based on the date that the IRB granted conditional approval of the protocol, not on the date that final approval is granted.

(c) Deferral. The deferral of a protocol action is due to substantive concerns or lack of clarity about the conduct of the protocol and/or safety of the subjects.

1 Deferral is appropriate whenever more information is needed before IRB members are prepared to recommend approval or disapproval.

2 The IRB Administrator will forward the IRB's specific and detailed stipulations and recommendations in writing to the Principal Investigator. When appropriate, the assigned HSPS

makes provisions for a telephone conversation about the identified issues, in order to help the investigator understand the required revisions or requested additional information.

3 The Principal Investigator must address all of the IRB's stipulations and recommendations before re-submitting the protocol to the IRB Office for coordination of re-review by the IRB.

4 In its consideration of revised materials, the IRB will focus on the responses of the investigator and determine if the revised protocol satisfies all the review requirements.

(d) Disapproval. The protocol is disapproved as currently written. Disapproval of a research plan will be communicated in writing by the HQ USAMRMC IRB Chair or designee, to the Principal Investigator, the CG, USAMRMC, and to other organizations as appropriate. This written notification will include a statement of the reasons for the IRB's decision and give the investigator an opportunity to respond in person or in writing. In order to ensure an investigator adequately understands the reasons for a protocol's disapproval, the IRB Chair, Administrator or the assigned HSPS will arrange a teleconference with the Principal Investigator to discuss the IRB's concerns. The prospects and conditions of eventual approval will be discussed candidly. Any protocol disapproved by the IRB may be resubmitted, but only with a complete summary of responses to all of the IRB concerns.

(8) Meeting Minutes. The IRB Administrator and the assigned HSPS (as well as a minutes-taker) record the Board's discussion, controverted issues and their resolution, and the Board's stipulations, recommendations and considerations. The HQ USAMRMC IRB meetings are also video and audio taped to verify the accuracy of the information discussed for purposes of inclusion in minutes of the meeting. These tapes are erased immediately after the minutes of a meeting are approved by the CG, USAMRMC. This generally occurs within a few weeks of the meeting.

6-10. Approval Authority of the HQ USAMRMC IRB and the Research Institution

32 CFR 219.112 states as follows:

Research covered by this policy that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB.

Thus, research subject to the HQ USAMRMC IRB's review may not be approved for implementation by any DOD official unless it has first been approved or recommended for approval by the IRB. An official at any level may not reject the HQ USAMRMC IRB's recommendation for disapproval, conditional approval, or deferral and may not approve that protocol for implementation, nor does any official have the authority to reduce or waive safeguards, restrictions, or stipulations that IRB recommends in a conditional approval (see 32 CFR 219.112; AR 70-25(3-2.e.(2)); AR 70-25-Appendix C-2.g).

6-11. Appeal Process

(a) Investigators may appeal the decisions of the HQ USAMRMC IRB to require modifications or to disapprove research, in writing, documenting the reasons for the appeal (within 30 days of the IRB's decision).

(b) Investigators shall provide the written appeal along with any supporting documents through their Institutional Official to the ORP IRB Office. The HQ USAMRMC IRB Chair (or Vice Chair/Acting Chair) will review the appeal and decide if additional information is necessary for consideration at an IRB meeting. The appeal will be brought to a convened meeting of the IRB, and the Principal Investigator will be invited to attend the meeting to present the protocol and address issues surrounding the appeal. Written notification of the HQ USAMRMC IRB's decision of the appeal will be sent to the Principal Investigator and his/her Commander following the meeting.

Chapter 7. Knowledge of Local Research Context

This chapter describes how the HQ USAMRMC IRB fulfills its responsibilities relative to ensuring that the IRB has adequate knowledge of local research context prior to approving research.

7-1. Background

a. The regulations at 32 CFR 219.103(d) require that the adequacy of IRBs be evaluated “in light of the anticipated scope of the institution’s research activities, the types of subject populations likely to be involved, . . . and the size and complexity of the institution.” Furthermore, 32 CFR 219.107(a) requires that IRBs be “(i) sufficiently qualified through . . . the diversity of the members, including consideration of race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel; and (ii) able to ascertain the acceptability of proposed research in terms of institutional commitments and regulations, applicable law, and standards of professional conduct and practice.”

b. The regulations also require that IRBs must be capable of ensuring that (i) selection of subjects is equitable; (ii) privacy of subjects is protected and confidentiality of data is maintained; (iii) informed consent is sought in language understandable to the subject and under conditions that minimize the possibility of coercion or undue influence; and (iv) appropriate safeguards protect the rights and welfare of vulnerable subjects (32 CFR 219.111(a)(3),(a)(4),(a)(7),(b), and 219.116).

7-2. Consideration of Local Research Context by the HQ USAMRMC IRB

a. The HQ USAMRMC IRB is geographically distant from the majority of Institutions for which it serves as IRB of record; this necessitates that the IRB members and ORP IRB Office staff be aware of and evaluate important site-related issues during its review of protocols. Among these considerations are the following:

- (1) The anticipated scope of the research activities;
- (2) The types of subject populations likely to be involved;
- (3) The size and complexity of the institution conducting the research;
- (4) Institutional commitments, regulations, and policies;
- (5) Applicable laws, including country, state and local laws;
- (6) Standards of professional conduct and practice;
- (7) Methods for equitable selection of subjects;
- (8) Methods for protection of privacy of subjects;
- (9) Methods for maintenance of confidentiality of data;
- (10) Language(s) understood by prospective subjects;

(11) Methods of minimizing the possibility of undue influence or coercion in seeking consent;

(12) Safeguards to protect the rights and welfare of vulnerable and special populations; and

(13) Cultural and religious considerations.

b. The HQ USAMRMC IRB will apply knowledge of the local research context to ensure that:

(1) Selection of subjects is equitable;

(2) Privacy of subjects is protected and confidentiality of data is maintained;

(3) Informed consent is sought in language understandable to the subject and under conditions that minimize the possibility of coercion or undue influence;

(4) Appropriate safeguards protect the rights and welfare of vulnerable subjects and special populations;

(5) Local cultural, religious and community norms are respected;

(6) As appropriate, the research provides enduring enhanced infrastructure or improved programs that are beneficial to the community.

c. The HQ USAMRMC IRB will obtain information about the local research context through one or more of the following mechanisms:

(1) Written materials;

(2) Discussions with appropriate consultants;

(3) Personal knowledge of the local research context on the part of IRB members and consultants through extended, direct experience with the research institution, its subject populations, and its surrounding community;

(4) Review of the proposed research by appropriate subject matter experts;

(5) Systematic and documented interchange between the HQ USAMRMC IRB, the ORP IRB Office, and the research institution. Such interchanges include, but are not limited to:

(a) Periodic visits to the research site;

(b) Periodic discussions with appropriate consultants knowledgeable about the local research context;

(c) Regular interactions with designated institutional liaisons such as the Human Protection Administrator (HPA);

(d) Review of relevant written materials such as institutional policies, guidance documents, memoranda, and standard operating procedures;

(e) Review of applicable state and local laws, as well as cultural standards and norms applicable to the study location and/or target population.

(f) Presentations to the IRB by institutional representatives regarding local target populations for research, site-specific cultural institutional practices and special safeguards in place for the protection of research participants.

d. Research reviewed by the HQ USAMRMC IRB is subject to state laws. The following are examples of state laws that may be relevant to research reviewed by the IRB:

- (1) Defining age of majority;
- (2) Reporting of abuse;
- (3) Reporting of infectious diseases;
- (4) Reporting of sepsis;
- (5) Defining who can serve as LAR.

Chapter 8. Criteria for Approval of Human Subjects Research

This chapter describes the criteria that must be met for the HQ USAMRMC IRB to recommend approval of a human subjects research study to the CG, USAMRMC. These criteria apply when human research is reviewed by either expedited or convened-Board review procedures.

8-1. Common Rule Approval Criteria (the “7 in 111”)

a. The HQ USAMRMC IRB determines that all of the following requirements set forth in 32 CFR 219.111 are satisfied:

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

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 32 CFR 219.116. (See Section 7-2)

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by 32 CFR 219.117. (See Section 7-3)

(6) When appropriate the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects.

(7) When appropriate there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

b. In addition, when some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as military service members, children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, the IRB will consider additional safeguards to protect the rights and welfare of these subjects.

8-2. Requirements for Informed Consent

a. The HQ USAMRMC IRB reviews the planned research activities to ensure that the informed consent process adequately describes how informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with and to the extent required by 32 CFR 219.116. The IRB reviews the informed consent document to determine whether it is consistent with the protocol plan, Investigator's brochure, and Sponsor's or Investigator's protocol, and contains the necessary elements of informed consent as required by the federal regulations.

b. Informed consent is an exchange of information between the research team and the study participants throughout the course of a research study. Informed consent must:

(1) Be solicited under conditions that minimize the possibility of undue influence or coercion;

(2) Use language understandable to the participant;

(3) Not waive or appear to waive participants' rights; and

(4) Include each of the required elements and applicable additional elements of informed consent describing the research and the nature of research participation as required by federal regulations:

(a) A clear statement that the study involves "research;"

(b) An explanation of the purposes of the research;

(c) The expected duration of the subject's participation;

(d) A complete description of the procedures to be followed, and identification of procedures that are performed as standard of care and identification of procedures that are performed solely for the purposes of research;

(e) A description of the reasonably foreseeable risks and discomforts;

(f) A description of any benefits to the participant or others that may reasonably be expected from the research;

(g) A disclosure of appropriate alternative procedures or courses of treatment that might be advantageous to the participant;

(h) A description of the extent to which confidentiality of records identifying the participant and privacy will be maintained;

(i) For research involving more than minimal risk, an explanation whether medical care is available in the event of a research related injury; who will be responsible for covering the cost of any such injury; and where further information may be obtained;

(j) An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject; and

(k) A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the participant is otherwise entitled, and the participant may discontinue participation at any time without penalty or loss of benefits to which the participant is otherwise entitled.

(5) Additional Consent Elements. The informed consent document should, where appropriate, include the following additional elements:

(a) For women of child bearing potential, a statement that the particular treatment or procedure may involve risks to the participant (or the embryo or fetus, if the participant is or may become pregnant) which are currently unforeseeable;

(b) Anticipated circumstances under which the subject's participation may be terminated by the Investigator without regard to the participant's consent;

(c) If there is the potential that costs of research procedures will not be paid by the sponsor or the participant's insurance, a description of any additional costs to the participant that may result from participation in the research;

(d) The consequences of a participant's decision to withdraw from the research and procedures for orderly termination of participation by the subject;

(e) A statement that significant new findings developed during the course of the research which may relate to the participant's willingness to continue participation will be provided to the participant;

(f) The approximate number of participants involved in the study; and

(g) Study treatment(s) and the probability of random assignment to placebo or to each treatment.

(6) The HQ USAMRMC IRB may require that information, in addition to that required in federal regulations, be given to research participants when in its judgment the information would meaningfully add to the protection of the rights and welfare of participants.

(7) The HQ USAMRMC IRB may request necessary revisions to the content, language, punctuation, and/or grammar in order for the intended target population to clearly understand the proposed research activities and make an informed decision on whether to participate in the research.

8-3. Waiver or Alteration of the Informed Consent Process

a. The HQ USAMRMC IRB ensures that provisions are made to obtain legally effective informed consent prospectively from each research participant or permission from his/her legally authorized representative. IAW 32 CFR 219.116d, the IRB may approve a consent procedure, which does not include, or which alters, some or all of the required elements of informed

consent, or waive the requirements to obtain informed consent entirely, provided the IRB finds and documents that:

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

b. The Principal Investigator is responsible for providing detailed justification that these four criteria are met.

c. Note: The criteria listed above for waiver or alteration of informed consent are not applicable to FDA-regulated research.

8-4. Documentation of Informed Consent for Human Subjects Research

a. Unless specifically waived or altered by the HQ USAMRMC IRB, there are two options for documentation of informed consent. The IRB will determine which of the procedures described below is appropriate for documenting informed consent in research applications that it reviews.

(1) Written consent form signed and dated by the participant or legally authorized representative.

(a) In most circumstances, the HQ USAMRMC IRB will require that informed consent is documented by the use of a written consent form approved by the IRB and signed by the participant or the participant's legally authorized representative.

(b) This consent form must embody, in language understandable to the participant, all the required elements necessary for legally effective informed consent. The required elements of informed consent as described in Section 8-2.b(4) of this document, in addition to any applicable additional elements that are required by the federal regulations must be included.

(c) The consent form may be read to the participant or the participant's legally authorized representative. However, the Investigator should allow the participant or the legally authorized representative adequate opportunity to read and consider the consent document before it is signed. A copy of the informed consent document must be given to the person signing the form.

(2) Oral presentation using short form.

(a) As an alternative to standard written informed consent documents, oral presentation of informed consent information may be used (e.g., with illiterate participants). The participant must be provided with both a short form written informed consent document stating that the required elements of consent have been presented orally to the participant or the participant's legally authorized representative; and a written summary of the information that is presented orally.

(b) A witness to the oral presentation is required. The witness must sign and date both the short form written informed consent document and a copy of the written summary.

(c) The participant or the legally authorized representative must sign and date the short form written consent document.

(d) The person obtaining consent (e.g., the Principal Investigator) must sign and date a copy of the written summary of the information that is presented orally. The person obtaining consent may not be the witness to the consent.

b. The HQ USAMRMC IRB may approve a process that allows the informed consent document to be delivered by mail or facsimile to the potential participant or the potential participant's legally authorized representative and to conduct the consent interview by telephone when the participant or the legally authorized representative can read the consent document as it is discussed. All other applicable conditions for documentation of informed consent must also be met when using this procedure.

c. Verbal agreement (e.g., consent obtained over the telephone) to participate in a research study is not permitted unless the documentation or process of informed consent is waived or altered by the IRB.

8-5. Waiver of Documentation of Informed Consent

The HQ USAMRMC IRB may waive the requirement for the Investigator to obtain a signed consent form for some or all participants. A waiver of documentation means that the requirement to obtain a *signed* consent document is waived, however, a consent process must still take place. The waiver of documentation is appropriate when telephone contact will be made with the subject or surveys will be sent to subjects (email/computer, postal service). The basic elements of informed consent (32 CFR 219.116 (a-b)) must be communicated to the subject verbally (if contact occurred by telephone) or in writing (as part of survey or information sheet provided to the subject), but a signed consent form is not required. In order to waive the requirement for documentation of informed consent the IRB must find either:

a. That the only record linking the participant and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality (32 CFR 219.117(c)(1)); or

b. That the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context (32 CFR 219.117(c)(2)).

(1) For FDA-regulated research, this condition cannot be used to justify waiver of documentation.

(2) In cases in which the documentation requirement is waived, the HQ USAMRMC IRB may require the Principal Investigator to provide participants with a written statement regarding the research.

8-6. Informed Consent and Non-English Speaking Participants

a. It is preferable that the written informed consent documents for non-English speaking participants embody, in a language understandable to the participant, all the required elements necessary for legally effective informed consent. Alternatively, the regulations permit oral presentation of informed consent information in conjunction with a short form written consent document (stating that the elements of consent have been presented orally) and a written summary of what is presented orally (32 CFR 219.117(b)(2)).

b. During the consent process an individual who is knowledgeable about the study and who can answer questions in the subjects' language or through a translator should be present. A witness to the oral presentation is required, and the participant must be given copies of the short form informed consent document and the summary. When this procedure is used with participants who do not speak English, the following are required:

(1) The oral presentation and the short form written informed consent document should be in a language understandable to the participant;

(2) The IRB-approved English language informed consent document may serve as the summary; and

(3) A witness who is fluent in both English and the language of the participant should be present.

c. 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 HQ USAMRMC IRB. 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 the following 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. The HQ USAMRMC IRB may also request a certified back-translation.

8-7. DOD-, Army-, and HQ, USAMRMC-Specific Review Requirements

To recommend research for approval, the HQ USAMRMC IRB must also consider whether the following DOD-, Army-, and USAMRMC-specific issues are adequately addressed:

a. **Limitation on the Use of Humans as Experimental Subjects.** The requirements of Title 10 United States Code (USC) 980 are given in the Definitions section of this document (Appendix B). Briefly, for experimental studies in which there is a plan to include subjects who are not capable of providing their own consent, the HQ USAMRMC IRB must determine that there is an intent to benefit each subject that will be enrolled in the trial.

b. **Requirement for a Medical Monitor.** Per DODD 3216.02 all greater than minimal risk (GTMR) studies require a medical monitor. The name of the medical monitor must be included in the protocol and CV must be provided to the HQ USAMRMC IRB, who will ensure that an appropriate individual is assigned.

(1) This individual should be a qualified physician, other than the Principal Investigator, not associated with the protocol, able to provide medical care to research volunteers for conditions that may arise during the conduct of the study, and who will monitor the volunteers during the conduct of the study.

(2) In some studies it may be acceptable to have a qualified health care provider other than a physician serve as medical monitor, depending upon the type of risk that might occur in the study (e.g., a clinical psychologist).

(3) The medical monitor plays a role in reviewing serious adverse events and unanticipated problems prior to submission to the HQ USAMRMC IRB. The IRB will review the proposed role of the medical monitor in protocol and determine if the role allows the medical monitor to remain independent from the study.

c. Requirement for an Ombudsman. The HQ USAMRMC IRB will give special consideration to the recruitment process for military personnel.

(1) During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an ombudsman, not connected in any way with the proposed research or the unit, shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate (DODD 3216.02, paragraph 4.4.4.).

(2) For research involving more than minimal risk and also involving military personnel, unit officers and noncommissioned officers (NCOs) may not influence the decisions of their subordinates to participate or not to participate as research subjects. Unit officers and senior NCOs in the chain of command may not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session (DODD 3216.02, paragraph 4.4.4.). Military personnel are trained to act as a unit, so peer pressure should also be considered and minimized if possible.

d. Payment for Study Participation for Active Duty Military Personnel. Under 24 USC 30, payment to active duty military personnel for participation in research is limited to blood donation and may not exceed \$50 per blood draw. Active duty research subjects may not receive any other payment for participation in a research study. This \$50 limitation applies only when active duty military personnel are participating while "on-duty." If they participate while off-duty (e.g., while on leave or after duty hours), then they may be compensated as are other research participants.

e. Confidentiality. Confidentiality risk assessment for military personnel requires serious consideration of the potential to affect the military career. Medical and psychological diagnoses can lead to limitation of duties or discharge. Information regarding alcohol or drug abuse, drunk driving, sexual or spousal abuse and sexual orientation can 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. For military volunteers, the consent form may need to contain a statement that complete confidentiality cannot be guaranteed because information bearing on an active duty member's health may be required to be reported to appropriate medical or command authorities.

f. Medical Care for Research Related Injury.

(1) Federal regulations governing human subjects research require that research subjects involved in GTMR research must be informed of the availability of medical treatment or compensation if a research-related injury occurs. This information should inform the subject if treatment is available, and if it is, what that consists of or where further information may be obtained (32 CFR 219.116).

(2) The applicable Army Regulation, AR 70-25 at paragraph 3-1 k, authorizes medical care for research subjects in Army MTFs. It also specifically authorizes contracting officers to negotiate costs of medical care coverage or medical care direct charges for extramural research conducted via contract or grant, but does not mandate that extramural researchers provide this coverage. Paragraph 3-56 of AR 40-400, an Army medical care regulation, reiterates the availability of MTF-based care for injuries to research subjects arising from the medical research. Neither regulation limits access to medical care to subjects participating in GTMR research protocols.

(3) The following language must be included in consent forms for Army managed GTMR studies:

“If you are hurt or get sick because of this research study, you can receive medical care at an Army hospital or clinic free of charge. You will only be treated for injuries that are directly caused by the research study. The Army will not pay for your transportation to and from the hospital or clinic. If you have questions about this medical care, talk to the principal investigator for this study, (name and telephone number of principal investigator). If you pay out-of-pocket for medical care elsewhere for injuries caused by this research study, contact the principal investigator. If the issue cannot be resolved, contact the U.S. Army Medical Research and Materiel Command (USAMRMC) Office of the Staff Judge Advocate (legal office) at (301) 619-7663/2221.”

Non-USAMRMC Army and other DOD institutions may have specific language that may be more appropriate for the consent form. This language can be negotiated on a case by case basis.

g. Volunteer Registry Management System (VRMS). USAMRMC maintains a database system that permits the identification of volunteers who have participated in GTMR research conducted by the USAMRMC and/or where an OTSG-sponsored investigational product is administered. This system was developed to ensure that research volunteers are adequately informed concerning the risks involved with their participation in research and to provide research volunteers with any newly acquired information that may affect their well-being when that information becomes available participation in research. The HQ USAMRMC IRB may waive the requirement for collection of the VRMS, and may also require completion of VRMS for other studies as it deems necessary.

Chapter 9. Special Populations

This chapter describes the HQ USAMRMC IRB's policies and procedures for the review and approval of research with (1) pregnant women and fetuses; (2) children; (3) cognitively impaired individuals; and (4) military members.

9-1. Background

a. Conducting research with special populations requires that investigators provide a rationale for involvement of vulnerable subjects, substantiate the decision to involve a vulnerable population, and explain why a less vulnerable population would not serve the purpose of the research. When special populations will be targeted for enrollment, the HQ USAMRMC IRB considers the provisions for additional protections for these populations in the Federal and DOD regulations for research, and assesses the safeguards proposed by the Principal Investigator to minimize the possible risks and the chance of harm involved in the study.

b. When considering a protocol that targets enrollment of subjects from a special population, the HQ USAMRMC IRB Chair, Vice Chair or designated IRB member will assess the needs for specialized expertise among the IRB membership to assure that the IRB possesses the professional competence necessary to review the specific research activities. The HQ USAMRMC IRB may invite non-voting individuals to assist in the review of issues which require expertise beyond, or in addition to, that available among IRB members.

9-2. Research with Pregnant Women and Fetuses

a. Research involving women who are or may become pregnant receives special consideration by the HQ USAMRMC IRB because of women's additional health concerns during pregnancy and because of the need to avoid unnecessary risk to the fetus. Further, in the case of a pregnant woman, the IRB must determine when informed consent of the father is required for research. Special attention is justified because of the involvement of a third party (the fetus) who may be affected but cannot give consent and because of the need to prevent harm or injury to future members of society. Procedural protections beyond the basic requirements for protecting human participants are prescribed in the federal regulations for research involving pregnant women.

b. Any study in which women of childbearing potential are subjects may inadvertently include pregnant women.

(1) Federal regulations require that, when appropriate, subjects be provided a statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus, if the subject is or may become pregnant) which are currently unforeseeable as part of the informed consent process.

(2) In some studies, the IRB may need to assure that nonpregnant subjects are advised to avoid pregnancy or nursing for a time during or following the research. Furthermore, where appropriate, subjects should be advised to notify the Principal Investigator immediately should they become pregnant.

(3) The HQ USAMRMC IRB will assess whether the mother's participation would pose any risk to the fetus or nursing infant.

(4) In some instances, there may be potential risk sufficient to justify requiring that pregnant women either be specifically excluded from the research or studied separately. However, while pregnant women are considered vulnerable participants, women of reproductive age should not be arbitrarily excluded from participation in research. If women will be excluded, such exclusion must be fully justified by the Principal Investigator based on scientific rationale.

c. In addition to the regulatory requirements established in 32 CFR 219, the HQ USAMRMC IRB considers the provisions of 45 CFR 46, Subpart B as follows when reviewing research with pregnant women as participants. Pregnant women or fetuses may be involved in research if all of the following conditions are met:

(1) Where scientifically appropriate, preclinical studies, including studies on pregnant animals, and clinical studies, including studies on nonpregnant women, have been conducted and provide data for assessing potential risks to pregnant women and fetuses; and

(2) The risk to the fetus is caused solely by interventions or procedures that hold out the prospect of direct benefit for the woman or the fetus; or if there is no such prospect of benefit, the risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge which cannot be obtained by any other means; and

(3) Any risk is the least possible for achieving the objectives of the research; and

(4) If the research holds out the prospect of direct benefit to the pregnant woman, the prospect of a direct benefit both to the pregnant woman and the fetus, or no prospect of benefit for the woman nor the fetus when risk to the fetus is not greater than minimal and the purpose of the research is the development of important biomedical knowledge that cannot be obtained by any other means, her consent is obtained in accord with the informed consent provisions in as described in Chapter 8 of this document; and

(5) If the research holds out the prospect of direct benefit solely to the fetus then the consent of the pregnant woman and the father is obtained in accord with the informed consent provisions described in Chapter 8 of this document, except that the father's consent need not be obtained if he is unable to consent because of unavailability, incompetence, or temporary incapacity or the pregnancy resulted from rape or incest; and

(6) Each individual providing consent under paragraphs 4 and 5 (above), is fully informed regarding the reasonably foreseeable impact of the research on the fetus or neonate; and

(7) For children who are pregnant, assent and permission are obtained in accord with the provisions described in Chapter 8 of this document; and

(8) No inducements, monetary or otherwise, will be offered to terminate a pregnancy; and

(9) Individuals engaged in the research will have no part in any decisions as to the timing, method, or procedures used to terminate a pregnancy; and

(10) Individuals engaged in the research will have no part in determining the viability of a neonate.

d. Neonates may be involved in research if all of the following conditions are met:

(1) Neonates of uncertain viability and nonviable neonates may be involved in research if all of the following conditions are met:

(a) Where scientifically appropriate, preclinical and clinical studies have been conducted and provide data for assessing potential risks to neonates; and

(b) Each individual providing consent under paragraph 2.b or 3.e (below) of this section is fully informed regarding the reasonably foreseeable impact of the research on the neonate; and

(c) Individuals engaged in the research will have no part in determining the viability of the neonate; and

(d) The requirements of paragraph 2 or 3 (below) of this section have been met as applicable.

(2) Neonates of uncertain viability. Until it has been ascertained whether or not a neonate is viable, a neonate may not be involved in research covered by this policy unless the following additional conditions have been met:

(a) The HQ USAMRMC IRB must determine that:

1. The research holds out the prospect of enhancing the probability of survival of the neonate to the point of viability, and any risk is the least possible for achieving that objective; or

2. The purpose of the research is the development of important biomedical knowledge which cannot be obtained by other means and there will be no added risk to the neonate resulting from the research; and

(c) The legally effective informed consent of either parent of the neonate, or if neither parent is able to consent because of unavailability, incompetence, or temporary incapacity, the legally effective informed consent of either parent's legally authorized representative is obtained in accord with the provisions described in Chapter 8 of this document, except that the consent of the father or his legally authorized representative need not be obtained if the pregnancy resulted from rape or incest.

(3) Nonviable neonates. After delivery a nonviable neonate may not be involved in research covered by this policy unless all of the following additional conditions are met:

(a) Vital functions of the neonate will not be artificially maintained; and

(b) The research will not terminate the heartbeat or respiration of the neonate; and

(c) There will be no added risk to the neonate resulting from the research; and

(d) The purpose of the research is the development of important biomedical knowledge that cannot be obtained by other means; and

(e) The legally effective informed consent of both parents of the neonate is obtained in accord with the provisions described in Chapter 8 of this document, except that the waiver alteration provisions do not apply. However, if either parent is unable to consent because of unavailability, incompetence, or temporary incapacity, the informed consent of one parent of a nonviable neonate will suffice to meet the requirements of this paragraph, except that the consent of the father need not be obtained if the pregnancy resulted from rape or incest. The consent of a legally authorized representative of either or both of the parents of a nonviable neonate will not suffice to meet the requirements of this paragraph.

(4) Viable neonates. If a neonate is judged viable (i.e. likely to survive to the point of sustaining life independently, given the benefit of available medical therapy), it is then called an infant and should be treated as a child for purpose of research participation. A neonate, after delivery, that has been determined to be viable may be included in research only to the extent permitted by and in accord with the requirements of 45 CFR 46, Subpart D (see Section 9-2).

e. Research involving (after delivery) the placenta, the dead fetus, or fetal material may be approved by the HQ USAMRMC IRB if all of the following conditions are met:

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

(2) If information associated with material described in paragraph f(1) (below) of this section is recorded for research purposes in a manner that living individuals can be identified, directly or through identifiers linked to those individuals, those individuals are research subjects and all pertinent subparts of the regulations are applicable.

f. Research involving transplantation of fetal tissue may be approved by the HQ USAMRMC IRB if all of the following conditions are met:

(1) Research involving the transplantation of human fetal tissue for therapeutic purposes may be conducted only if the woman providing the tissue makes a statement, in writing and signed by the woman, declaring that:

(a) The woman donates the fetal tissue for research; and

(b) The donation is made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue; and

(c) The woman has not been informed of the identity of any such individuals.

(2) Research involving the transplantation of human fetal tissue for therapeutic purposes may be conducted only if the attending physician with respect to obtaining the tissue from the woman involved makes a statement, in writing and signed by the attending physician, declaring that:

(a) In the case of tissue obtained pursuant to an induced abortion:

1. The consent of the woman for the abortion was obtained prior to requesting or obtaining consent for a donation of the tissue for use in such research; and

2. No alteration of the timing, method, or procedures used to terminate the pregnancy was made solely for the purposes of obtaining the tissue; and

3. The abortion was performed in accordance with applicable State law; and

(b) The tissue has been donated by the woman in accordance with paragraph 1 (above) of this section; and

(c) Full disclosure has been provided to the woman with regard to:

1. Such physicians interest, if any, in the research to be conducted with the tissue; and

2. any known medical risks to the woman or risks to her privacy that might be associated with the donation of the tissue and that are in addition to risks of such type that are associated with the woman's medical care.

(3) Research involving transplantation of human fetal tissue for therapeutic purposes may be conducted only if the Principal Investigator makes a statement in writing and signed by the Principal Investigator, declaring that the Principal Investigator:

(a) Is aware that:

1. The tissue is human fetal tissue; and

2. The tissue may have been obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth; and

3. The tissue was donated for research purposes; and

(b) The Principal Investigator has provided such information to other individuals with responsibilities regarding the research; and

(c) The Principal Investigator will require, prior to obtaining the consent of an individual to be a recipient of a transplantation of the tissue, written acknowledgment of receipt of such information by such recipient; and

(d) The Principal Investigator has had no part in any decisions as to the timing, method, or procedures used to terminate the pregnancy made solely for the purpose of the research.

(4) Research involving transplantation of human fetal tissue for therapeutic purposes may be conducted only if the head of the agency or other entity conducting the research involved certifies to the DDR&E that the statements required under paragraphs 2 and 3 (above) of this section will be available for audit by the Director.

(5) Research involving transplantation of human fetal tissue for therapeutic purposes may be conducted only if it is conducted in accordance with applicable federal, State and local laws and institutional policies and procedures.

9-3. Research with Children

a. Children have special vulnerability as research subjects. To safeguard the interests and to protect children from harm, special ethical and regulatory considerations apply for reviewing research involving children; these are specified in 45 CFR 46, Subpart D as follow. The HQ USAMRMC IRB may approve research involving children only if these special provisions are met.

(1) When reviewing research involving children, the HQ USAMRMC IRB classifies the research into one of four categories and documents their discussions of the risks and benefits of the research study. The four categories of research involving children that may be approved by the IRB are based on degree of risk and benefit to individual subjects:

(a) Research not involving greater than minimal risk to children (45 CFR 46.404). When the HQ USAMRMC IRB finds that no greater than minimal risk to children is presented, the IRB may approve the research only if the IRB finds that adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians, as set forth below in Section b.

(b) Research involving GTMR but presenting the prospect of direct benefit to the individual child (45 CFR 46.405). If the HQ USAMRMC IRB finds that more than minimal risk to children is presented by an intervention or procedure that holds out the prospect of direct benefit for the individual child, or by a monitoring procedure that is likely to contribute to the child's well-being, the IRB may approve the research only if the IRB finds that:

1. The risk is justified by the anticipated benefit to the children;
2. The relation of the anticipated benefit to the risk is at least as favorable to the children as that presented by available alternative approaches; and
3. Adequate provisions are made for soliciting the assent of the children and permission of their parents or legal guardians, as set forth below in Section b.

(c) Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child's disorder or condition (45 CFR 46.406). If the HQ USAMRMC IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual child, or by a monitoring procedure which is not likely to contribute to the well-being of the child, the IRB may approve the research only if the IRB finds that:

1. The risk represents a minor increase over minimal risk;
2. The intervention or procedure presents experiences to participants that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;
3. The intervention or procedure is likely to yield generalizable knowledge about the participants' disorder or condition which is of vital importance for the understanding or amelioration of the participants' disorder or condition; and

4. Adequate provisions are made for soliciting assent of the children and permission of their parents or legal guardians, as set forth below in Section b.

(d) Research not otherwise approvable, which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children (45 CFR 46.407). If the HQ USAMRMC IRB finds the research does not meet the requirements set forth in categories 46.404, 46.405 or 46.406 as described above, the IRB may approve the research only if:

1. The IRB finds that the research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and

2. The DDR&E after consultation with a panel of experts in pertinent disciplines (for example: science, medicine, education, ethics, law) and following opportunity for public review and comment, has determined either:

(a) That the research in fact satisfies the conditions of categories 46.404, 46.405, or 46.406; or

(b) The research presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; the research will be conducted in accordance with sound ethical principles; and adequate provisions are made for soliciting the assent of children and the permission of their parents or legal guardians, as set forth below in Section b.

(2) The HQ USAMRMC IRB must determine if the proposed study holds the prospect of direct benefit for participants and document their discussions of the potential benefits of the research study as it relates to the requirements of the Subpart and 10 USC 980. The HQ USAMRMC IRB will assess the Principal Investigator's stated intent to benefit each subject enrolled into the study.

b. Requirements for Permission by Parents or Legal Guardians and for Assent by Children.

(1) Adequate Provisions for Child's Assent. IAW 45 CFR 46.408, the HQ USAMRMC IRB must find and document that adequate provisions are made for soliciting the assent of child participants when in the judgment of the IRB the children are capable of providing assent.

(a) In determining whether children are capable of assenting, the HQ USAMRMC IRB will take into account the ages, maturity, and psychological state of the children involved. This judgment may be made for all children to be involved in research under a particular protocol, or for each child, as the IRB deems appropriate. The child should be given an explanation of the proposed research procedures in a language that is appropriate to the child's age, experience, maturity, and condition. In determining the capacity of a child to provide assent the HQ USAMRMC IRB will assess:

1. The conduct and demeanor at the time consent is to be given;

2. The totality of the circumstances;

3. The nature of the proposed research procedures and their risks, probable consequences, benefits, and alternatives to the treatment; and

4. The child's ability to appreciate the nature, risks, consequences, benefits, and alternatives of the proposed research procedures.

(b) Waiver of Assent. If the HQ USAMRMC IRB determines either of the following to be true, then the assent of the children is not a necessary condition for proceeding with the research:

1. The capability of some or all of the children is so limited that they cannot reasonably be consulted; or

2. The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the children and is available only in the context of the research.

(a) Therefore, when the research offers the child the possibility of a direct benefit that is important to the health or well-being of the child and is available only in the context of the research, the IRB may determine that the assent of the child is not necessary.

(b) Additionally, in such circumstances, a child's dissent which should normally be respected, may be overruled by the child's parents at the IRB's discretion. When research involves the provision of experimental therapies for life-threatening diseases such as cancer, however, the IRB should be sensitive to the fact that parents may wish to try anything, even when the likelihood of success is marginal and the probability of extreme discomfort is high. Should the child not wish to undertake such experimental therapy, difficult decisions may have to be made. In general, if the child is a mature adolescent and death is imminent, the child's wishes should be respected.

(c) Finally, even where the HQ USAMRMC IRB determines that the child participants are capable of assenting, the IRB may still waive the assent requirement under circumstances in which consent may be waived for adults in accordance with the provisions described in Chapter 8 of this document regarding waiver or alteration of informed consent generally.

(c) Adequate Provisions for Parents' or Legal Guardians' Permission. The HQ USAMRMC IRB must find that adequate provisions are made for soliciting the permission of each child's parents or legally authorized representative.

1. Research not involving greater than minimal risk to children. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research not involving greater than minimal risk.

2. Research involving greater than minimal risk but presenting the prospect of direct benefit to the individual child. Where parental permission is to be obtained, the IRB may find that the permission of one parent is sufficient for research involving greater than minimal risk but presenting the prospect of direct benefit to the individual participants when the provisions of Section b above are met.

3. Research involving greater than minimal risk and no prospect of direct benefit to the individual child, but likely to yield generalizable knowledge about the child's disorder or condition. When permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

4. Research not otherwise approvable which presents an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children. When permission is to be obtained from parents, both parents must give their permission unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child.

(d.) Waiver of Parental or Legal Guardian Permission. If the HQ USAMRMC IRB determines that a research protocol is designed for conditions or for a participant population for which parental or legally authorized representative permission is not a reasonable requirement to protect the participants (for example, neglected or abused children), it may waive the consent requirements described above, provided all of the following are true:

1. An appropriate mechanism for protecting the children who will participate as subjects in the research is substituted. The choice of an appropriate mechanism would depend upon the nature and purpose of the activities described in the protocol, the risk and anticipated benefit to the research participants, and their age, maturity, status, and condition;

2. The research is not subject to FDA regulations; and

3. The waiver is not inconsistent with federal, state, or local law.

(2) Documentation.

(a) Permission by parents or legal guardians shall be documented in the same manner as required for participants under the provisions described in Chapter 8 of this document.

b. When the IRB determines that assent of a child is required, it shall also determine whether and how assent must be documented.

9-4. Research with Cognitively Impaired Persons

a. Persons with cognitive impairment have diminished autonomy and special vulnerability as research subjects. To safeguard their interests and to protect these subjects from harm, the HQ USAMRMC IRB applies special ethical and regulatory considerations when reviewing research involving cognitively impaired subjects.

b. For subjects where there is the potential for cognitive impairment, the HQ USAMRMC IRB will review the protocol to determine the measures used to determine potential subjects' ability to provide voluntary informed consent.

c. For adult subjects who lack the capacity to provide their own informed consent, the subjects' legally authorized representatives may grant permission on their behalf for participation in research. Family members and close friends are not considered legally authorized representatives (LAR) for the adult subject unless they have been formally appointed as that person's health care agent, legal guardian or conservator.

d. Requirements for Permission by LAR and for Assent by Persons with Cognitive Impairment.

(1) Legally authorized representatives may grant permission for subjects who are unable to provide voluntary informed consent to take part in research. The HQ USAMRMC IRB will review the process of obtaining permission from such representatives to ensure it adheres to the same standards as the informed consent process for subjects (see Chapter 8).

(2) Studies may take place over extended periods of time and subjects may lose the ability to provide consent during that period, or conversely may gain the capacity to provide consent (i.e., subjects become cognitively impaired or their cognitive impairment may improve). The HQ USAMRMC IRB will consider whether and when periodic re-consenting of individuals or their LAR is required to assure that a subject's continued involvement is voluntary. The IRB may require that the Principal Investigator re-consent subjects after taking into account the study's anticipated length and the condition of the individuals to be enrolled (e.g., subjects with traumatic brain injuries, progressive neurological disorders, etc.). Additionally, the HQ USAMRMC IRB considers whether and when to require reassessment of decision-making capacity.

(3) The HQ USAMRMC IRB determines and documents that adequate provisions are made for soliciting the assent of subjects when, in the judgment of the IRB, subjects with cognitive impairment are capable of providing assent.

(a) In determining whether potential subjects are capable of assenting, the HQ USAMRMC IRB will take into account the psychological state and any concurrent injury, medical condition or medication that the subjects may be taking either for medical or research purposes. This judgment may be made for all subjects to be involved in research under a particular protocol, or for each subject, as the IRB deems appropriate. The potential subject should be given an explanation of the proposed research procedures in a language that is appropriate to the subject's level of understanding.

(b) If the HQ USAMRMC IRB determines either of the following to be true, then the assent of the cognitively impaired subject is not a necessary condition for proceeding with the research:

1. The capability of some or all of the subjects is so limited that they cannot reasonably be consulted; or

2. The intervention or procedure involved in the research holds out a prospect of direct benefit that is important to the health or well-being of the subject and is available only in the context of the research.

9-5. Research Involving Military Personnel

a. Military personnel may be under unique constraints compared to other research participants, affecting their ability to make a truly voluntary and un-coerced decision whether or not to participate as subjects in research. To safeguard their interests and to protect military personnel from research harms, special ethical and regulatory considerations apply for reviewing research involving military personnel. The HQ USAMRMC IRB may approve research involving military personnel only if the following special provisions are met:

(1) The HQ USAMRMC IRB must find that research involving military personnel as participants addresses additional considerations for military personnel as determined by DOD, Army, USAMRMC and any local regulations.

(2) For research involving military personnel, the HQ USAMRMC IRB will apply the definition of minimal risk IAW 32 CFR 219.i, i.e., “. . . the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” “Daily life” in the definition of minimal risk is interpreted in terms of the daily life of the age-matched general population, not the study target population (e.g. Special Forces Soldiers).

(3) The HQ USAMRMC IRB will consider the following criteria during review of protocols that target enrollment of military personnel:

(a) The risks involved in the research are commensurate with risks that would be encountered by age-matched non-military volunteers;

(b) Any possible advantages accruing to the military member through his or her participation in the research, when compared to duty assignments, favorable acknowledgments, general living conditions, medical care, and other conditions, are not of such a magnitude that his or her ability to weigh the risks of the research against the value of such advantages is impaired;

(c) Procedures for the selection of participants are fair and immune from arbitrary intervention by personnel in the military members’ chain of command;

(d) The research procedures or outcomes will not adversely affect military members’ deployability during or after study completion; and

(e) Where the HQ USAMRMC IRB finds there may be a need for follow-up examination or care of participants after the end of their participation, adequate provision has been made for such examination or care.

(f) When a military member is also a member of another special population (e.g., a minor, pregnant woman, or a person with cognitive impairment), the additional policies in this chapter will also apply.

(4) As appropriate, the additional considerations for including military personnel as research subjects that will be considered by the HQ USAMRMC IRB include those described in Chapter 8-7(c), (d) and (e) of this document regarding the requirement for an ombudsman, reducing undue influence by the chain of command, confidentiality and payment for study participation.

Chapter 10. The Health Insurance Portability and Accountability Act (HIPAA)

10-1. Background and Definitions

a. HIPAA was enacted by the U.S. Congress in 1996. Title I of HIPAA protects health insurance coverage for workers and their families when they change or lose their jobs. Title II of HIPAA, known as the Administrative Simplification (AS) provisions, requires the establishment of national standards for electronic health care transactions and national identifiers for providers, health insurance plans, and employers.

b. Privacy Rule. Title II of HIPAA contains the Privacy Rule which requires covered entities to notify individuals of uses of their private health information (PHI). Covered entities must keep track of disclosures of PHI and document privacy policies and procedures.

c. Security Rule. Title II of HIPAA contains the Security Rule which deals specifically with Electronic Protected Health Information (EPHI). The Security Rule identifies security standards for three types of safeguards required for compliance with HIPAA: administrative, physical, and technical. For each of these, the Security Rule identifies standards and implementation specifications that must be adopted and administered.

d. Covered Entity. A health plan, a health care clearinghouse, or a health care provider who transmits health information and is therefore subject to the HIPAA regulations. Research health information (as defined below) is not considered part of the covered entity.

e. PHI. Individually identifiable health information that is or has been collected or maintained by the covered entity in the course of providing healthcare that can be linked back to the individual participant.

f. Research Health Information (RHI). Individually identifiable health information that is or has been collected solely for the purposes of research.

g. Disclosure of PHI. The release, transfer, or provision of access to, or divulging in any manner of information outside of the covered entity.

h. Use of PHI. Querying, viewing, and/or extracting any protected health information for research purposes within the covered entity.

i. Authorization. A customized document that gives an Investigator permission to use specified PHI for a specific purpose, or to disclose PHI to a third party specified by the Investigator other than for treatment, payment or healthcare operations.

j. Individually Identifiable Health Information. Any information collected from an individual (including demographics) that is created or received by a health care provider, health plan, employer, and/or health care clearinghouse that relates to the past, present or future physical or mental health or condition of an individual, or the provision of health care to an individual or the past, present or future payment for the provision of health care to an individual and identifies the individual and/or to which there is reasonable basis to believe that the information can be used to identify the individual.

k. Limited Data Set. PHI that excludes direct identifiers of the individual or of relatives, employers, or household members of the individual, with the exception of city, state, ZIP Code, elements of dates, and other numbers, characteristics, or codes not listed as direct identifiers.

l. Anonymous Data. Information that was previously recorded or collected without any of the 18 identifiers as defined by HIPAA and no code is assigned which would allow data to be traced to an individual.

m. Coded Information/Data. For the purposes of this policy, identifying information that would enable the Investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

n. De-identified Health Information. Health information that has been stripped of all 18 identifiers as defined by HIPAA so that the information could not be traced back to an individual. De-identified data also pertains to health information that has been assigned and retains a code or other means of identification provided that:

(1) The code is not derived from or related to the information about the individual;

(2) The code could not be translated to identify the individual; and

(3) The covered entity (as described above) does not use or disclose the code for other purposes or disclose the mechanism for re-identification.

o. Designated Record Set. A group of records maintained by a covered entity that includes medical and billing records about an individual for the purpose of treatment, payment, or provision of health care. Research records that are not contained in the participant's medical record are not likely to be a part of the designated record set.

p. Data Use Agreement. An agreement between institution issuing the PHI and the recipient of the PHI. This agreement establishes who is permitted to use or receive the limited data set, and provides that the limited data set recipient will:

(1) Not use or further disclose the information other than as permitted by the data use agreement or as otherwise required by law;

(2) Use appropriate safeguards to prevent use or disclosure of the information other than as provided for by the data use agreement;

(3) Report to the covered entity any use or disclosure of the information not provided for by its data use agreement of which it becomes aware;

(4) Ensure that any agents, including a subcontractor, to whom it provides the limited data set agrees to the same restrictions and conditions that apply to the limited data set recipient with respect to such information; and

(5) Not identify the information or contact the individuals.

q. Minimum Necessary Standard. The least information reasonably necessary to accomplish the intended purpose of the use, disclosure, or request of PHI.

r. Preparatory to Research. Any action taken in assessing the research question or hypothesis, such as accessing medical records, querying of databases for any type of individually identifiable health information, or any activity where PHI is accessed to prepare a research protocol.

10-2. HQ USAMRMC IRB Review of HIPAA Authorizations, Waivers and Alterations

a. The HQ USAMRMC IRB will review and approve HIPAA authorizations and requests for waivers or alterations of HIPAA authorization for covered entities relying on the HQ USAMRMC IRB that do not have established privacy boards in accordance with 45 CFR 160 and 164. The HQ USAMRMC IRB will not review and approve HIPAA authorizations or requests for waivers or alterations in HIPAA authorization for institutions that have an established privacy board.

b. Research Use or Disclosure of PHI with Authorization. A Principal Investigator must obtain an authorization from all participants in research prior to the use or disclosure of PHI for any research-related purpose not otherwise permitted or required under this policy. A legally effective authorization must include the following:

(1) A specific and meaningful description of the information to be used or disclosed;

(2) The name or identification of the persons or class of persons authorized to make or receive disclosures of PHI and to use the PHI for research-related purposes;

(3) An expiration date or event, or a statement such as “end of research study” or “none” when appropriate (e.g., for a research database);

(4) A statement that the individual may revoke the authorization if requested in writing to the Principal Investigator. However, the Principal Investigator may continue to use and disclose, for research integrity and reporting purposes, any PHI collected from the individual, pursuant to such authorization before it was revoked;

(5) A statement that an individual’s clinical treatment may not be conditioned upon whether the individual signs the research authorization;

(6) A statement that information disclosed under the authorization could potentially be re-disclosed by the recipient and would no longer be protected under HIPAA; and

(7) The individual’s signature (or that of his or her legally authorized representative) and date.

c. Waiver or Alteration of Authorization.

(1) In some circumstances, research authorizations otherwise required under this policy may be waived or altered, provided the HQ USAMRMC IRB determines that the following criteria are satisfied and documented:

(a) The use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals, based on the presence of at least the following elements:

1. An adequate plan to protect the identifiers from improper use and disclosure;
2. An adequate plan to destroy the identifiers at the earliest opportunity consistent with the conduct of the research, unless there is a health or research justification for retaining the identifiers or such opportunity consistent with the conduct of the retention is otherwise required by law; and
3. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of PHI would be permitted by this Policy;

(b) The research could not practicably be conducted without the waiver or alteration;
and

(c) The research could not practicably be conducted without access to and use of the PHI.

(2) Disclosures of PHI made pursuant to a waiver are subject to the minimum necessary standard.

(3) In accordance with 45 CFR 164.528, individuals have the right to request and receive an accounting from the covered entity of all possible disclosures of his/her protected health information that was permitted without the individual's authorization. If a protocol is granted a waiver of authorization by the HQ USAMRMC IRB, the Principal Investigator must be prepared to provide the covered entity's privacy office the following information for all PHI disclosed:

(a) The date of the disclosure;

(b) The name, title, and contact number of the covered entity member making the disclosure;

(c) The name of the entity or person who received the protected health information, and, if known, the address of such entity or person;

(d) A brief description of the protected health information disclosed; and

(e) A brief statement of the purpose of the disclosure that reasonably describes the basis for disclosure.

d. Use or Disclosure of "De-identified" Health Information.

(1) De-identified health information is exempt from HIPAA regulations and may be used or disclosed for research purposes without a HIPAA authorization or HQ USAMRMC IRB waiver of authorization.

(2) Investigators must provide documentation to the HQ USAMRMC IRB that the health information has been de-identified by one of the following two methods:

(a) Statistical Method: The HQ USAMRMC IRB may determine that health information is de-identified for purposes of this policy, if an independent, qualified statistician:

1. Determines that the risk of re-identification of the data, alone or in combination with other data, is very small; and

2. Documents the methods and results by which the health information is de-identified, and the expert makes his or her determination of risk. Note: the expert may not be the Principal Investigator or anyone directly involved in the research study.

(b) Removal of All Identifiers. Identifiers concerning the individual and the individual's employer, relatives and household members that must be removed include: names; geographic subdivisions smaller than a state; ZIP codes; dates directly related to an individual; telephone numbers; fax numbers; electronic mail addresses; social security numbers; medical record numbers; health plan beneficiary identifiers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; web universal resource locators (URL); internet protocol (IP) address numbers; biometric identifiers, including finger and voice prints; full face photographic images; and any other number, characteristic or code that could be used to identify the individual.

(c) The de-identified information (as described in the definition above) may be assigned a re-identification code that can be affixed to the research record to permit the information to be re-identified if necessary, provided:

1. The key to such a code is not accessible to the Principal Investigator requesting to use or disclose the de-identified health information; and

2. The code is not derived from any of the 18 HIPAA identifiers.

e. Limited Data Sets.

(1) A Principal Investigator may use or disclose a limited data set for research purposes without a HIPAA authorization or waiver of authorization.

(2) A limited data set must exclude all of the following direct identifiers of the individual or of the individual's employer, relatives, or household members: names; postal address information other than town or city, state, and ZIP code; telephone numbers; fax numbers; electronic mail addresses; social security numbers; medical record numbers; health plan beneficiary identifiers; account numbers; certificate/license numbers; vehicle identifiers and serial numbers, including license plate numbers; device identifiers and serial numbers; web URL; IP address numbers; biometric identifiers, including finger and voice prints; full face photographic images and any comparable images; and any other number, characteristic or code that could be used to identify the individual.

(3) A limited data set may be used or disclosed only if there is a data use agreement between the covered entity and the recipient of the limited data set.

f. Participant's Access to Research Information. Individuals who participate in research have a right to access their own PHI that is maintained in a Designated Record Set. However, individuals participating in research protocols that include treatment may be denied access to their PHI obtained in connection with that research protocol, provided that:

- (1) The PHI was obtained in the course of the research;
- (2) The individual agreed to the denial of access in the research authorization;
- (3) The research remains in progress; and

(4) The individual's rights to access such PHI are re-instated once the research study has ended and the research authorization has expired.

g. **Participant's Request to Revoke Research Authorization.** An individual may revoke his or her authorization, in writing, to the Principal Investigator at any time. However, the Principal Investigator may continue to use and disclose for research integrity and reporting purposes, any PHI collected about the individual pursuant to a valid authorization before it was revoked.

h. **Use and Disclosure of PHI Without Authorization When it is Preparatory to Research.** A Principal Investigator may use or disclose PHI without HQ USAMRMC IRB review for the development of a research protocol, provided that all of the following criteria are satisfied:

(1) The use or disclosure of PHI is solely to prepare a research protocol, or to identify prospective research participants for purposes of seeking an authorization;

(2) The Investigator shall not record or remove the PHI from the covered entity; and

(3) The PHI sought is necessary for the purposes of the research.

i. **Use and Disclosure of Decedent's PHI Without Authorization.** A Principal Investigator may use and disclose decedents' PHI for research purposes without HQ USAMRMC IRB review provided that all of the following criteria are satisfied:

(1) The use will be solely for research about the decedents;

(2) The PHI sought is necessary for the purposes of the research; and

(3) The Principal Investigator has documentation of the death of the individuals about whom information is being sought.

Chapter 11. Research Using the Internet

a. The HQ USAMRMC IRB must review all research activities involving the use of the internet with the same considerations and standards for approval of research, informed consent, and voluntary participation as all other research activities.

(1) The informed consent process, and documentation of consent, must include all relevant elements of informed consent as listed in the federal and DOD regulations (see Chapter 8).

(2) The HQ USAMRMC IRB will consider the risks to the participants and determine if there is an appropriate level of protection.

(a) The IRB will consider that each communication carries the risk of a breach of confidentiality. Even when data is collected without names, web sites or email programs may still be capable of collecting identifying information such as IP addresses.

(b) The IRB will consider the screening procedures for potential participants that will be conducted through electronic means (e.g., methods to verify age if the study requires age restrictions).

(c) If the research involves special populations, the HQ USAMRMC IRB will consider all additional requirements outlined in Chapter 9.

(3) The use of online surveys must include mechanisms, if applicable, for:

(a) Withdrawal from study participation and removal of responses from a participant who has decided to withdraw, if applicable;

(b) Allowing participants to refuse to provide responses to particular questions, as applicable.

(4) Because there is no standard for identifying distressed participants online, the HQ USAMRMC IRB will take into consideration potential participant experiences (e.g., the sensitive nature of the research) that may be distressing when evaluating the risk/benefit ratio.

b. Requirements for Evaluating the Use of the Internet for Participant Recruitment.

(1) The HQ USAMRMC IRB must review and approve all materials used for posting recruitment materials on the internet (e.g., through a website, a banner advertisement, or an email solicitation) (see Chapter 12).

(2) There are a variety of listing services that post information about research opportunities for potential participants. If this method is used in recruitment of potential participants, the material submitted to the HQ USAMRMC IRB for review must include information on the site used to advertise or list the study and the language that will be posted as an advertisement.

(3) If use of the internet is proposed as a method of recruitment or for other study-related purposes after initial approval of the protocol by the HQ USAMRMC IRB, the intended use must be submitted as an amendment to the already approved proposal (see Chapter 15).

c. Requirements for Consideration of Data Collection and Security.

(1) All data must be protected as it moves along the communication pathways (e.g., from the participant to the server, from the server to the Investigator). Additionally, all databases storing identifiable information or data must be protected regardless of the source creating the data (e.g., encryption of the database, de-identifying the data).

(2) The HQ USAMRMC IRB must review and approve the method and procedures for data collection and security.

(3) Investigators must provide information in the protocol regarding the transmission and storage of the data.

(4) If a Principal Investigator chooses to use a separate server for data collection or storage, the HQ USAMRMC IRB must review and approve its administration.

Chapter 12. Recruitment and Advertising

12-1. Equitable Selection of Subjects

The inclusion of women, men, and minorities in research is important, both to ensure that they receive an appropriate share of the benefits of research and that they do not bear a disproportionate burden. To the extent that participation in research offers direct benefits to the participants, under-representation of men, women or minorities denies them the opportunity to benefit. Moreover, for purposes of generalizing research results, investigators must include the widest possible range of population groups. For these reasons, recruitment methods should be designed to take into account the need to attract eligible subjects representing both genders and minority groups, unless the research is clearly targeted to a specific group (e.g. prostate cancer)

12-2. Review of Recruitment Methods and Advertisements

a. The HQ USAMRMC IRB must assure that appropriate safeguards exist to protect the rights and welfare of research subjects. In fulfilling these responsibilities, the IRB reviews all research documents and activities, including the methods and materials that Investigators propose to use to recruit participants.

b. The HQ USAMRMC IRB considers advertising or soliciting for study participants to be the start of the informed consent process and subject selection process. Advertisements must be reviewed and approved by the IRB as part of the package submitted for initial review.

c. When the Principal Investigator decides to advertise for participants following the HQ USAMRMC IRB's initial approval of the protocol, the advertising is considered an amendment to the ongoing study.

d. When advertising is to be used, the HQ USAMRMC IRB must review the information contained in the advertisement and the mode of its communication to determine that it does not present an undue inducement, is not coercive, and does not state or imply a certainty of favorable outcome or other benefits beyond what is specified in the consent document and the protocol. The IRB must review the final copy of printed advertisements. When advertisements are to be taped for broadcast, the HQ USAMRMC IRB must review the final audio or video tape. The HQ USAMRMC IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording.

e. The HQ USAMRMC IRB reviews recruitment methods and advertising to ensure that it does not promise a certainty of treatment outcome beyond what is outlined in the consent and the protocol. This is especially critical when a study may involve participants who are likely to be vulnerable to undue influence.

(1) Investigators must obtain HQ USAMRMC IRB approval for all print, television, radio, or videotape advertisements, e-mail solicitations, Internet web sites, and other recruitment methods and materials intended for the recruitment of prospective research participants prior to their use.

(2) Any advertisement used to recruit participants should be limited to the information the prospective participants need to determine their eligibility and interest. When appropriately worded, the following may be included in advertisements:

- (a) The purpose of the research, and if applicable, the condition under study;
- (b) The criteria that will be used to determine eligibility for the study. Ideally this will be concisely presented in summary form;
- (c) A brief list of participation benefits, if any. NOTE: payment for participation is not a benefit of participation;
- (d) The time or other commitment required of the participants; and
- (e) The location of the research and the person or office to contact for further information; and the name, address, and facility or institution of the Investigator or study coordinator.

(3) Advertising materials should not include the following:

- (a) Claims, either explicitly or implicitly, that the drug, biologic, device or other type of intervention is safe or effective for the purposes under investigation;
- (b) Claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic, device or intervention;
- (c) Terms such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational, i.e., not approved for general consumption by the FDA; or
- (d) Promises of “free medical treatment,” when the intent is only to say that participants will not be charged for taking part in the investigation.

f. Additional recruitment requirements:

(1) Telephone Screening. The first contact prospective study participants may have is with a study staff person on the telephone. A script used to discuss or screen potential participants to determine basic eligibility for the specific study is often used. The HQ USAMRMC IRB must review the procedures and scripts used to ensure that they adequately protect the rights and welfare of the prospective participants. Additionally, the IRB will evaluate any information collected about prospective participants to ensure it is collected in accordance with applicable human subjects protection regulations.

2) Internet Recruitment. All advertisements and recruitment methods must be reviewed and approved by the HQ USAMRMC IRB prior to implementation except for specific clinical trial listing services that do not require prospective IRB approval as determined by the FDA. These include the National Cancer Institute’s cancer clinical trial listing (PDQ), the government-sponsored Acquired Immune Deficiency Syndrome (AIDS) ACTIS, and the National Institutes of Health (NIH) listing at clinicaltrials.gov. For other Internet recruitment sites, HQ USAMRMC IRB review and approval is required prior to implementation.

(3) Mass Communication E-mails. Advertising submitted through mass email solicitation must be reviewed and approved by the HQ USAMRMC IRB prior to implementation. Email solicitations should be simple, readable, and understandable. Information in the solicitation should conform to the requirements for written advertisements (see paragraph e above).

(4) Recruitment Using Databases and Health Care Providers. Investigators may request to use search methods of particular databases to identify potential participants that may be eligible for research projects (e.g., search by disease, age, sex, etc.), or they may request to contact health care providers for access to potential participants from the provider's patient population. Such recruitment methods require HQ USAMRMC IRB approval prior to initiation.

Chapter 13. Research with Human Specimens and Data

a. Investigators who wish to obtain, use or analyze any specimens or data obtained from humans for research purposes must submit the proposed project description (in sufficient detail) to the ORP IRB Office prior to initiation of the study. The ORP IRB Office will determine if the proposed effort meets the regulatory definition of “research” and then determine if the research involves human subjects. If the project is determined to meet the definition of research involving human subjects, the ORP IRB Office will then determine if it meets the criteria for exemption from IRB review, or if the research study must be submitted for either expedited or convened HQ USAMRMC IRB review (see Chapter 6).

b. The ORP IRB Office or HQ USAMRMC IRB will review the use of previously obtained human specimens and data for undefined future research purposes to ensure the use is consistent with the originally approved protocol and consistent with the expectations of the specimen/data donor (for example, if subjects signed an informed consent document stating their specimens/data would be used for future studies to examine cancer development processes, the subjects could not have reasonably expected that their specimens/data would be used to test mechanisms of anthrax resistance).

c. Activities that would not be considered to involve human subjects include, but are not limited to:

(1) Receiving and/or using specimens or data that have been permanently stripped of individually identifiable information (no code housed anywhere).

(2) Use of a publicly available, unidentifiable, cell lines or databases.

(3) Receiving coded private information or specimens provided the following conditions are met:

(a) The code is not derived from or related to the identifiable information that must be stripped from the private information (e.g. patient medical record number + last 4 digits of the individual’s Social Security number);

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

(c) The Principal Investigator cannot readily ascertain the identity of the individuals to whom the coded private information or specimens pertain, because:

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

2. The Principal Investigator and the holder of the key enter into an agreement prohibiting the release of the key to the Investigator under any circumstances, until the individuals are deceased;

3. The private information is received from an IRB-approved repository or data management center that includes written operating procedures that prohibit the release of the key to the Investigator under any circumstances, until the individuals are deceased; or

4. There are other legal requirements prohibiting the release of the key to the Principal Investigator until the individuals are deceased.

d. Repositories. A repository is a storage site and mechanism by which identifiable human tissue, blood, genetic material or data are stored or archived for future use in research by multiple investigators or multiple research projects.

(1) Specimen and/or data extraction from an existing repository requires determination of the regulatory status of the proposed research (i.e. “not research”, “research not involving human subjects,” exempt, non-exempt) by the ORP IRB Office prior to extraction of the specimens or data. If not exempt, the specimen and/or data use will require review and approval by the HQ USAMRMC IRB under a specific protocol.

(2) Investigators who wish to obtain and store specimens or data for future research purposes should consider establishing a research “repository.”

(3) Investigators who establish repositories that will be accessed by others are encouraged to develop Standard Operating Procedures pertaining to the maintenance and withdrawal of specimens and/or data.

(4) The ORP IRB Office and HQ USAMRMC IRB does not consider the act of solely providing coded private information or specimens from a repository to constitute human subjects research. Note that if the individuals who provide coded information or specimens for research collaborate on other activities related to the conduct of the research with the investigators who receive such information or specimens, then such additional activities would be considered to constitute human subjects research. Examples of such additional activities include, but are not limited to: (a) the study, interpretation, or analysis of the data resulting from the coded information or specimens; and (b) authorship of presentations or manuscripts related to the research.

(5) Investigators who wish to prospectively collect data and samples to add to an existing specimen or data repository must seek HQ USAMRMC IRB approval to do so.

(6) The HQ USAMRMC IRB does not oversee the storage or management of specimens or data that are collected and stored as part of routine clinical care or hospital procedures, nor does it oversee the use or management of specimens or data sent to an Investigator for specialized analysis as part of a contractual agreement.

Chapter 14. HQ USAMRMC IRB Review of Contingency INDs for Force Health Protection

a. Background. DOD Instruction (DODI) 6200.02, "Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs," describes responsibilities for implementation of 10 United States Code (USC) 1107 ("Notice of Use of an Investigational New Drug or a Drug Unapproved for its Applied Use") and prescribes the process for review and approval of DOD contingency IND protocols for FHP. The DOD FHP program is an organized program of healthcare preventive or therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions. Within DODI 6200.02, the USAMRMC Human Subjects Research Review Board (now the HQ USAMRMC IRB) is designated as the IRB of record for review and approval of the DOD contingency IND protocols for FHP. These protocols undergo initial and continuing IRB review and approval, and are available to be implemented if needed.

b. 10 USC 1107 (as released on 18 March 2004). Information regarding the notice of use of an IND or a drug unapproved for its applied use and waiver of informed consent is contained in 10 USC 1107 and is quoted below:

"§ 1107. Notice of use of an investigational new drug or a drug unapproved for its applied use

(a) Notice Required.—

(1) Whenever the Secretary of Defense requests or requires a member of the armed forces to receive an investigational new drug or a drug unapproved for its applied use, the Secretary shall provide the member with notice containing the information specified in subsection (d).

(2) The Secretary shall also ensure that health care providers who administer an investigational new drug or a drug unapproved for its applied use, or who are likely to treat members who receive such a drug, receive the information required to be provided under paragraphs (3) and (4) of subsection (d).

(f) Limitation and Waiver.—

(1) In the case of the administration of an investigational new drug or a drug unapproved for its applied use to a member of the armed forces in connection with the member's participation in a particular military operation, the requirement that the member provide prior consent to receive the drug in accordance with the prior consent requirement imposed under section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355 (i)(4)) may be waived only by the President. The President may grant such a waiver only if the President determines, in writing, that obtaining consent—

(A) is not feasible;

(B) is contrary to the best interests of the member; or

(C) is not in the interests of national security.

(2) In making a determination to waive the prior consent requirement on a ground described in subparagraph (A) or (B) of paragraph (1), the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior consent requirement on that ground."

c. Authority of the HQ USAMRMC IRB in the Review of Contingency INDs for FHP. Paragraph E4.4 of DODI 6200.02 designates the HQ USAMRMC IRB as the IRB responsible for review the contingency protocols for FHP. No local review is required but it may be conducted. No changes are permitted that require less information or remove procedures. Local modifications that preserve the core protocol and add site-specific procedures are acceptable. All locally modified documents must be submitted to the HQ USAMRMC IRB for review and approval.

d. Use of INDs for FHP. DODI 6200.02 establishes guidance for compliance with FDA requirements for INDs given at 21 CFR 312. The Secretary of the Army, as Executive Agent, in concert with the Commander of the Combatant Command involved and the Assistant Secretary of the Army for Health Affairs, develop a specific treatment protocol for use of the IND. The protocol is approved by the HQ USAMRMC IRB as a duly constituted IRB under 21 CFR 56. The only exceptions to the Instruction are cases where the Secretary of Defense requests a waiver of informed consent and the waiver is approved by the President of the United States under 10 USC 1107. The review of FHP INDs, therefore, has special significance for the HQ USAMRMC IRB. Any request from a Combatant Commander that involves use of an investigational product (and concomitant protocol) for FHP, with or without a request for waiver of informed consent, must be approved by the HQ USAMRMC IRB.

e. 21 CFR 50.23. The criteria for Presidential waiver of prior informed consent for the use of FHP INDs are described in 21 CFR 50.23(d) and are quoted below from this regulation.

"(1) Under 10 U.S.C. 1107(f) the President may waive the prior consent requirement for the administration of an investigational new drug to a member of the armed forces in connection with the member's participation in a particular military operation. The statute specifies that only the President may waive informed consent in this connection and the President may grant such a waiver only if the President determines in writing that obtaining consent: Is not feasible; is contrary to the best interests of the military member; or is not in the interests of national security. The statute further provides that in making a determination to waive prior informed consent on the ground that it is not feasible or the ground that it is contrary to the best interests of the military members involved, the President shall apply the standards and criteria that are set forth in the relevant FDA regulations for a waiver of the prior informed consent requirements of section 505(i)(4) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 355(i)(4)). Before such a determination may be made that obtaining informed consent from military personnel prior to the use of an investigational drug (including an antibiotic or biological product) in a specific protocol under an investigational new drug application (IND) sponsored by the Department of Defense (DOD) and limited to specific military personnel involved in a particular military operation is not feasible or is contrary to the best interests of the military members involved, the Secretary of Defense must first request such a determination from the President and certify and document to the President that the following standards and criteria contained in paragraphs (d)(1) through (d)(4) of this section have been met.

(i) The extent and strength of evidence of the safety and effectiveness of the investigational new drug in relation to the medical risk that could be encountered during the military operation supports the drug's administration under an IND.

(ii) The military operation presents a substantial risk that military personnel may be subject to a chemical, biological, nuclear, or other exposure likely to produce death or serious or life-threatening injury or illness.

(iii) There is no available satisfactory alternative therapeutic or preventive treatment in relation to the intended use of the investigational new drug.

(iv) Conditioning use of the investigational new drug on the voluntary participation of each member could significantly risk the safety and health of any individual member who would decline its use, the safety of other military personnel, and the accomplishment of the military mission.

(v) A duly constituted institutional review board (IRB) established and operated in accordance with the requirements of paragraphs (d)(2) and (d)(3) of this section, responsible for review of the study, has reviewed and approved the investigational new drug protocol and the administration of the investigational new drug without informed consent. DOD's request is to include the documentation required by § 115(a)(2).

(vi) DOD has explained:

(A) The context in which the investigational drug will be administered, e.g., the setting or whether it will be self-administered or it will be administered by a health professional;

(B) The nature of the disease or condition for which the preventive or therapeutic treatment is intended; and

(C) To the extent there are existing data or information available, information on conditions that could alter the effects of the investigational drug.

(vii) DOD's recordkeeping system is capable of tracking and will be used to track the proposed treatment from supplier to the individual recipient.

(viii) Each member involved in the military operation will be given, prior to the administration of the investigational new drug, a specific written information sheet (including information required by 10 U.S.C. 1107(d)) concerning the investigational new drug, the risks and benefits of its use, potential side effects, and other pertinent information about the appropriate use of the product.

(ix) Medical records of members involved in the military operation will accurately document the receipt by members of the notification required by paragraph (d)(1)(viii) of this section.

(x) Medical records of members involved in the military operation will accurately document the receipt by members of any investigational new drugs in accordance with FDA regulations including part 312 of this chapter.

(xi) DOD will provide adequate follow-up to assess whether there are beneficial or adverse health consequences that result from the use of the investigational product.

(xii) DOD is pursuing drug development, including a time line, and marketing approval with due diligence.

(xiii) FDA has concluded that the investigational new drug protocol may proceed subject to a decision by the President on the informed consent waiver request.

(xiv) DOD will provide training to the appropriate medical personnel and potential recipients on the specific investigational new drug to be administered prior to its use.

(xv) DOD has stated and justified the time period for which the waiver is needed, not to exceed one year, unless separately renewed under these standards and criteria.

(xvi) DOD shall have a continuing obligation to report to the FDA and to the President any changed circumstances relating to these standards and criteria (including the time period referred to in paragraph (d)(1)(xv) of this section) or that otherwise might affect the determination to use an investigational new drug without informed consent.

(xvii) DOD is to provide public notice as soon as practicable and consistent with classification requirements through notice in the Federal Register describing each waiver of informed consent determination, a summary of the most updated scientific information on the products used, and other pertinent information.

(xviii) Use of the investigational drug without informed consent otherwise conforms with applicable law.

(2) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must include at least 3 nonaffiliated members who shall not be employees or officers of the Federal Government (other than for purposes of membership on the IRB) and shall be required to obtain any necessary security clearances. This IRB shall review the proposed IND protocol at a convened meeting at which a majority of the members are present including at least one member whose primary concerns are in nonscientific areas and, if feasible, including a majority of the nonaffiliated members. The information required by § 56.115(a)(2) of this chapter is to be provided to the Secretary of Defense for further review.

(3) The duly constituted institutional review board, described in paragraph (d)(1)(v) of this section, must review and approve:

(i) The required information sheet;

(ii) The adequacy of the plan to disseminate information, including distribution of the information sheet to potential recipients, on the investigational product (e.g., in forms other than written);

(iii) The adequacy of the information and plans for its dissemination to health care providers, including potential side effects, contraindications, potential interactions, and other pertinent considerations; and

(iv) An informed consent form as required by part 50 of this chapter, in those circumstances in which DOD determines that informed consent may be obtained from some or all personnel involved.

(4) DOD is to submit to FDA summaries of institutional review board meetings at which the proposed protocol has been reviewed.

(5) Nothing in these criteria or standards is intended to preempt or limit FDA's and DOD's authority or obligations under applicable statutes and regulations."

To approve such a request, the HQ USAMRMC IRB will review and, if appropriate, will approve the requested protocol. As with any other protocol, HQ USAMRMC IRB will examine the relative risks and benefits of the product and must approve of the information to be provided to the service member. The waiver of the informed consent is not a waiver against informing; and, in fact, the regulation focuses on the information provided to both service members and health care providers. The HQ USAMRMC IRB must review and approve the information sheet to be provided to service members. Service members are to be informed of the risks and benefits associated with the product, potential side effects, and other pertinent information about the appropriate use of the drug (e.g., the directions on how to take the product). The IRB will also review the adequacy of the plan to disseminate information to potential recipients. Additionally, an informed consent document will also be submitted for review in the event that consent can be obtained from some of the potential participants. Finally, the HQ USAMRMC IRB will review the adequacy and plans for providing information to health care providers.

Upon review and approval by the HQ USAMRMC IRB of a request for using a product with a waiver of informed consent, the minutes of the HQ USAMRMC IRB meeting along with the protocol and plans, are submitted to the FDA. In accordance with Executive Order 13139, the Secretary of Defense, in consultation with the FDA, develops the waiver request for the President's signature. The request and supporting documents are reviewed by the Assistant to the President for National Security Affairs and the Assistant to the President for Science and Technology to ensure that the standards and criteria in 10 USC 1107 and 21 CFR 50.23(d) are met. The President will approve or deny the waiver request and will provide written notification of the decision to the Secretary of Defense and the FDA Commissioner. Unless a request to withdraw the request is submitted, the waiver remains in effect for one year and requires annual review and approval to remain in effect.

Chapter 15. Protocol Life Cycle Issues: Amendments, Continuing Review and Closure

15-1. Amendments

a. 32 CFR 219.103((4)(iii) requires written procedures that the IRB will follow to ensure prompt reporting to the IRB of proposed changes in a research activity and for ensuring that such changes in approved research during the period for which IRB approval has already been given may not be initiated without IRB review and approval, except when necessary to eliminate apparent immediate hazards to the subject.

b. Any changes (i.e., amendment, modification, revision) to the protocol must be submitted to the HQ USAMRMC IRB for review and approval prior to implementation of the change. If the amendment involves changes to the protocol, a revised protocol should be submitted with the amendment.

c. Responsibilities of Principal Investigator Regarding Proposed Changes in Approved Protocol. The Principal Investigator will obtain approval from the IRB for all proposed changes in previously approved research activities prior to implementing such changes (except when necessary to eliminate apparent immediate hazards to the subject). These include, but are not limited to, any modification or amendment of the protocol, the informed consent process, the test instruments, the recruitment materials, or change of the Principal Investigator. The submission for proposed changes should include a revised protocol, identifying the version by date in the header or footer of each page. A request identifying the proposed changes and the rationale for the modifications must accompany the revised protocol.

d. Scientific review of proposed changes may be required if the design of the research study has changed significantly by modification of the protocol.

e. Major Modifications/Amendments to Research not Eligible for Expedited Review. A major modification to an approved study may impact the risk/benefit ratio in the study, and may alter a subject's choice to remain enrolled. Consequently, for studies not eligible for expedited review, these types of modifications require full Board review. Some common examples of major modifications include the following:

- (1) Escalation in a drug(s) dosage(s).
- (2) Introduction of an additional drug(s).
- (3) Inclusion of a new invasive procedure.
- (4) Inclusion of more subjects; new populations.
- (5) Inclusion of additional performance sites on a case by case basis.

f. Minor Modifications to Research Not Eligible for Expedited Review. Minor modifications to a study that was reviewed by full Board may be reviewed and approved by the expedited review process (see 32 CFR 219.110(b)(2)). Some common examples of minor modifications include the following:

- (1) Changes in study staff members.

(2) Changes in contact information.

(3) Inclusion of advertisement material.

g. Modifications to Research Reviewed Via Expedited Procedure For no greater than minimal risk (NGTMR) studies that were previously eligible for expedited review, major or minor modifications may be reviewed by expedited review procedure provided the revised protocol continues to (1) present no greater than minimal risk to participants and (2) comprise one or more of the research categories in the Federal Register list of categories of research that may be reviewed by the IRB through an expedited review procedure.

h. Protocol Exceptions. A protocol exception is a request made by the Principal Investigator for a deviation from the approved study for a single subject or a small group of subjects; it is not a permanent revision to the research protocol. As for all amendments, a protocol exception must be approved by the HQ USAMRMC IRB prior to its implementation.

(1) A request for a protocol exception must be reviewed and approved by the convened HQ USAMRMC IRB (or the IRB Chair, Vice Chair or designated IRB member for protocols eligible for expedited review) prior to implementation of the planned protocol change. Examples of protocol exception requests include, but are not limited to:

(a) A request to enroll a research subject who fails to meet all of the protocol eligibility criteria. The subject may have been evaluated for all other parameters, and it was determined that not meeting this inclusion criteria or laboratory screening value would not cause harm to the subject or alter the validity of the study.

(b) A request to change, add, or delete certain protocol procedures for a subject for reasons that relate to the subjects safety and well-being.

(2) The HQ USAMRMC IRB will review the request for protocol exception in order to determine that it does not increase the risk to the subject(s), or jeopardize the integrity of the research data. The IRB may request documentation that the study sponsor (and FDA, if applicable) has evaluated the request for protocol exception.

(3) The IRB may grant approval, conditionally approve, defer, table, or disapprove the protocol exception.

(4) Documentation of sponsor (or FDA) approval and HQ USAMRMC IRB approval of the exception should be maintained in the Investigator's research study file.

(5) Multiple requests for exceptions on the same protocol require that the Principal Investigator submit an amendment request.

i. Instituting Unapproved Changes in Approved Research (see also Chapter 18). Implementing unapproved changes in a HQ USAMRMC IRB-approved protocol (except when necessary to eliminate apparent immediate hazards to the subject) is in violation of 32 CFR 219. If implementation of an unapproved change is suspected, ORP IRB Office staff in coordination with the HQ USAMRMC IRB Chair will investigate the matter and generate a report. Read-ahead packets for subsequent IRB review will include the original report and any supporting documentation. In addition, read-ahead packets will include an explanation of why the violation

occurred, and a recommended corrective action plan demonstrating how a repeat occurrence of such violation(s) will be prevented in the future.

If, as a result of verification efforts by the HQ USAMRMC IRB, unapproved deliberate changes (as opposed to unintended protocol deviations) are found to have been instituted, the IRB will examine the severity of the non-compliance to determine if it is serious and/or continuing (see Chapter 18) and discuss appropriate sanctions and/or required re-training to prevent future noncompliance.

15-2. Continuing Review of Research

a. 32 CFR 219.109(e) requires that “an IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research.” The review criteria for continuing review of protocols are the same as for initial review (see Chapter 8).

b. After the initial review and approval of proposed research involving human subjects, the HQ USAMRMC IRB retains responsibility for oversight of the project, including review of periodic reports, safety, and other updates, and monitoring for compliance with the protocol and applicable human subjects protection regulations. The IRB can withdraw or continue its approval of the research or require modifications to ensure that the original criteria for approval are still satisfied, namely, determinations as to the risks, potential benefits, adequate informed consent, and safeguards in the conduct of the protocol. The major issues to be considered at each periodic review as well as at the time of each safety or other update are whether, in light of the latest information, the risk/benefit ratio is still acceptable and if the informed consent is still adequate for the protection of the rights and welfare of the participating subjects. One key criterion to be examined is whether the consent process provides all the information that subjects would reasonably want or need to know in light of the issues identified during the protocol’s previous approval period.

c. Continuing Review Report.

(1) The Principal Investigator will regularly prepare and submit reports to the HQ USAMRMC IRB summarizing the progress of the research at intervals designated in the IRB’s approval of the research, but no less often than annually, as required at 32 CFR 219.109(e).

(2) Pursuant to 32 CFR 219.103(b)(4) and 21 CFR 56.108(a) investigators must submit a protocol summary and status report on the progress of the research to the IRB for periodic continuing review that includes (1) the number of subjects accrued, withdrawn, or discontinued, and the reasons; (2) a summary of any unanticipated problems involving risks to subjects or others, any AEs and any complaints about the research; (3) a summary of any recent literature, findings obtained thus far, amendments or modifications to the research since the last review, multi-center trial reports, especially any from Data Safety Monitoring Boards (DSMBs) or Data Monitoring Committees (DMCs), and any other relevant information, especially information about risks associated with the research; and (4) any statements of significant new findings provided to subjects, the current and any proposed new informed consent document, and the current Investigators’ brochure, if there is one (for all IND and Investigational Device Exemption (IDE)) studies) (see 21 CFR 312.33; AR 70-25 (2-9c)).

d. Continuing Review of Research by the HQ USAMRMC IRB.

(1) Research that was initially approved via expedited review may be reviewed for continuation through an expedited review procedure provided it still (1) presents no greater than minimal risk to participants and (2) comprises one or more of the research categories in the Federal Register list of categories of research that may be reviewed by the IRB through an expedited review procedure. The investigator must submit to the ORP IRB Office a continuing review report as outlined above, along with a current version of the protocol and consent form(s). These submissions should arrive at the ORP IRB Office at least 30 calendar days prior to the protocol's expiration date.

(2) Research identified to pose GTMR to subjects and research that poses NGTMR but does not appear in the categories of research that can be reviewed via an expedited review procedure will be reviewed and approved by the convened HQ USAMRMC IRB prior to continuation. These submissions should arrive at the ORP IRB Office at least 45 calendar days prior to the protocol's expiration date.

(3) Research reviewed and approved for continuation within the 30 day period prior to its expiration date may retain the previously established expiration date for its next continuing review. For example, if a protocol's expiration date is 1 February, and the protocol is reviewed and approved for continuation for a one-year period on 15 January, the new expiration date may be set at 1 February of the following year (rather than resetting the date to 15 January). Keeping the same anniversary date aids investigators in planning for continuing review at the same time each year.

e. Review Criteria for Continuing Review. The review criteria for continuing review of human research protocols are the same as those for initial review (i.e., IAW 32 CFR 219.111).

(1) The review of the protocol must be substantive and meaningful. In conducting continuing review of research not eligible for expedited review, the same primary reviewer system as for initial convened HQ USAMRMC IRB reviews will be employed as previously described. The ORP IRB Office provides all Board members with a complete read-ahead packet for continuing reviews. The IRB members receive and review the Principal Investigator's continuing review report, along with a current version of the protocol and consent form(s) prior to the IRB meeting. The minutes of the HQ USAMRMC IRB meetings will record separate deliberations, actions, and votes for each protocol undergoing continuing review and identify the period of re-approval.

(2) At the time of re-approval, the HQ USAMRMC IRB may limit the approval for a term of less than one year if the IRB determines there is reason to do so. The date when approval expires will be noted in the notification letter. After the IRB's re-approval, the informed consent documents, stamped with the date of expiration of approval, will be provided to the Principal Investigator. For subject consent purposes, photocopies of this consent form with the stamped approval period will be used. The date of approval of continuation by the convened IRB determines the date by which the next annual review must be accomplished. Delay in completion of any required modifications will not move the expiration date or extend the approval period.

f. "Full-Board" Initial Review Followed by "Expedited" Continuing Review. Categories (8) and (9) in the Federal Register list of categories of research permit an IRB to conduct expedited continuing review, subsequent to a full Board initial review.

(1) Category (8): Continuing review of research previously approved by the convened IRB as follows:

(a) where the research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or

(b) where no subjects have been enrolled and no additional risks have been identified;
or

(c) where the remaining research activities are limited to data analysis.

Note: Category (8) identifies three situations in which research that is GTMR and was initially reviewed by the convened IRB may undergo subsequent continuing review by an expedited review procedure.

(2) Category (9): Continuing review of research, not conducted under an IND application or IDE where categories (2) through (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves NGTMR and no additional risks have been identified. Thus, for research not conducted under an IND or IDE, category (9) specifically permits continuing review to be done by expedited procedure, subsequent to a full Board initial review, where the following three conditions are met:

(a) Categories (2) – (8) in the list of categories of research do not apply, and

(b) No additional risks have been identified in research during the initial approval period,
and

(c) The IRB determines that research presents NGTMR to participants.

g. Lapsed Approval.

(1) The HQ USAMRMC IRB cannot consider reinstatement of a study past its expiration date. If a study is not re-approved by its expiration date, the Principal Investigator will immediately be notified by the ORP IRB Office, and all study activities must cease except for those activities required to prevent placing subjects at risk.

(2) Once a protocol lapses approval, it must undergo approval by either expedited or full Board as is appropriate to its risk level and whether or not it is eligible for expedited review (See Section 6-8) before any further study activities (including subject enrollment, data collection and/or data analysis) may resume. The Principal Investigator must submit the full protocol, consent form(s) and all supporting documents as well as the continuing review report for the previous approval period for consideration by the HQ USAMRMC IRB.

15-3. Protocol Closure/Final Study Report

a. 32 CFR 219.103(b)(4)(iii) states, “Assurances applicable to federally supported or conducted research shall at a minimum include: ... written procedures which the IRB will follow...for ensuring prompt reporting to the IRB of proposed changes in a research activity...” One of these procedural requirements (32 CFR 219.103(b)(4)) is ensuring “prompt reporting to

the IRB of changes in a research activity.” The completion of the study is a change in activity and must be reported to the IRB. A final report/notice to the IRB allows it to close its files and provides information that may be used by the IRB in the evaluation and approval of related studies.

b. When a project is terminated or completed, the Principal Investigator will submit to the HQ USAMRMC IRB a protocol summary and a final report of the results of the research (no later than the end of the current approval period). The final report must include a summary of what was learned, and to what extent the project met its goals. In addition, the report must include: (a) the date of proposed study closure (b) the reason for closure (e.g., completed, terminated) (b) the number of subjects (or specimens/data) accrued; (c) a summary of AEs and any unanticipated problems involving risks to subjects or others; (c) a summary of any withdrawal of subjects from the research or complaints about the research since the last IRB review; (e) a summary of all protocol amendments implemented during the study period; (f) a summary of relevant recent literature, interim findings, and amendments or modifications to the research since the last review; (g) any relevant multi-center trial reports; (h) any other relevant information, especially information about newly discovered risks associated with the research; and (i) a copy of the last informed consent document (if applicable). The final report should address the plans for retention, disposal or future use of any research materials generated in the course of the study (e.g., data collected for the study, biologic, or chemical samples, etc.).

c. Completion shall mean the end of subject recruitment and all subject interactions and the completion of any planned experiments, analyses, or manipulations of research materials. Any retention of research materials or planned, contemplated, or potential uses of them not already specified and approved in a current project must be reviewed and approved by the HQ USAMRMC IRB as a new protocol.

d. When to Close a Research Protocol to Continuing HQ USAMRMC IRB Review.

(1) For a protocol to be closed from continuing IRB review, it is essential that, in that protocol, the research activity has indeed ended. This includes completion of data analyses and reporting of study findings. Studies that have not reached that stage of completion may not be closed.

(2) Prior to conclusion of the study, the Principal Investigator must coordinate with the medical monitor, if applicable, for any required medical follow-up and/or debriefing of volunteers. Principal Investigators need to be aware that once a protocol is closed, it must be formally reopened only as a new protocol.

e. Three Distinct Closure Categories Defined by ORP IRB Office.

(1) Protocol Withdrawal. A study is defined as withdrawn if it is closed voluntarily by the Principal Investigator in the early phase when: (i) the protocol has been received by the ORP IRB Office but has not yet been reviewed; (ii) protocol is currently under review by the IRB but has not yet been approved; or (iii) protocol has been approved, but no study procedures involving human subjects have been initiated.

(2) Protocol Termination. A study is defined as terminated if it is closed voluntarily or involuntarily by the Principal Investigator or the IRB for reasons such as: (a) due to human subject protection issues, such as the occurrence of events that raise safety concerns about the study; (b) due to non-compliance issues; (c) if the Principal Investigator started a research

project pending award of funding support, then learns that funding will not be made available and as a result is forced to terminate the project; (d) because of subject recruitment problems; (e) termination by the Sponsor; and/or (f) when early data analysis leads to determination that further research would be futile or that the study intervention is successful and no further study is necessary.

(3) Protocol Completion. A study is defined as completed if it is closed voluntarily by the Principal Investigator when: (a) the study is closed to further enrollment of subjects and all subjects have completed all research-related interventions and follow-up; (b) the research team has completed all of the specific aims including data collection and analyses as identified in the research protocol; and (c) the Principal Investigator has submitted the final report(s).

Note: Certain studies previously approved by full-Board review that do not yet qualify for closure as described above may qualify for an expedited review. A protocol may be approved by expedited continuing review (a) where the research is permanently closed to the enrollment of new subjects; all subjects have completed all research-related interventions; and the research remains active only for long-term follow-up of subjects; or (b) where no subjects have been enrolled and no additional risks have been identified; or (c) where the remaining research activities are limited to data analysis.

Chapter 16. Reporting Unanticipated Problems and Adverse Events, Deviations, and Knowledge of Pending Compliance Inspections to the HQ USAMRMC IRB

16-1. Reporting Requirements

a. 32 CFR 219.103 (5) requires written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head of (i) any unanticipated problems involving risks to subjects or others or any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB and (ii) any suspension or termination of IRB approval.

b. The events that must be reported to the IRB are specified in the federal regulations at 21 CFR 56.104(c), 21 CFR 56.108(a)(3), 21 CFR 56.108(b)(1), and 21 CFR 56.108(b)(2). Further, as a criterion for its approval of research, an IRB may require, when appropriate, that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (32 CFR 219.111(a)(6) and 21 CFR 56.111(a)(6)).

c. Reporting responsibilities of the Principal Investigator to the HQ USAMRMC IRB are specified in the protocol document, "Investigator Agreement: Responsibilities of the Principal Investigator in Human Research" that is signed by the Principal Investigator as part of the protocol approval process.

d. Events that the Principal Investigator must report promptly or immediately are detailed in the following sections. For the purposes of this policy, prompt reporting means providing initial notification of an event as quickly as possible after it has been identified. It is acknowledged that although circumstances may prevent immediate notification of reportable events, all required reporting must occur without delay. Investigators should contact the ORP IRB Office with any questions about the interpretation of what events require reporting to the IRB.

16-2. Unanticipated Problems and Adverse Events: Background

a. Unanticipated problems are those problems that may arise and are not described in the protocol or other study documents.

b. "Unanticipated Problems Involving Risks to Subjects or Others" (UPIRTSOs) is a broader category than Serious Adverse Events (SAEs), and may include issues other than adverse drug reactions, such as problems with overdosing or drug abuse, loss of control of research agents, patient data, or hazardous materials, psychological reactions, breach of confidentiality, economic risks, less than ideal results of treatment, etc. The criteria for whether such occurrences need to be acted on and perhaps reported to the department or other authorities are the same as for any SAEs or traditional safety report (32 CFR 219.103(b)(5)(i)), (21 CFR 56.108(b)(i)). The HQ USAMRMC IRB will decide if these reported events are truly part of the risks of daily living or routine medical care and thus implicitly anticipated. 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.

c. The only regulatory citation regarding reporting of AEs to the IRB is given at 21 CFR 812.150(a)(1). It states that an investigator shall submit to the Sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as

soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

d. Theoretically, the IRB is not required to receive AE reports other than those that are UPIRTSOs as per 32 CFR 219.103(b)(5)(i) and 21 CFR 56.108(b)(1).

e. As a criterion for its approval of research, an IRB may require when appropriate, that the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects (32 CFR 219.111(a)(6) and 21 CFR 56.111(a)(6)). What this means is that the IRB may require the investigator to evaluate all AEs to ensure the safety of the subjects.

f. The events that are required to be reported to the IRB are given at 32 CFR 219.103(b)(4)(iii), 32 CFR 219.103(b)(5)(i), 21 CFR 56.104(c), 21 CFR 56.108(a)(3), 21 CFR 56.108(b)(1), and 21 CFR 56.108(b)(2). These citations contain no mention of AEs.

16-3. UPIRTSO, SAE and AE Reporting Responsibilities of the Principal Investigator to the HQ USAMRMC IRB

a. In an effort to fulfill the HQ USAMRMC IRB's responsibility for monitoring and oversight of research, all UPIRTSOs, SAEs and all subject deaths must be promptly reported by telephone (301-619-2165), by email (IRBOFFICE@amedd.army.mil), or by facsimile (301-619-4165) to the ORP IRB Office. A complete written report must follow the initial notification.

b. If there is a medical monitor assigned to the protocol, the medical monitor is required to review reports of serious adverse events/UPIRTSOs and provide an unbiased written report of the event. At a minimum, the medical monitor should comment on the outcomes of the event or problem and, in the case of an AE or death, comment on the relationship to participation in the study. The medical monitor should also indicate whether s/he concurs with the details of the report provided by the study investigator.

c. Any information regarding SAEs or unanticipated problems received from other sites on multi-site protocols should also be provided to the HQ USAMRMC IRB for review.

d. In addition to prompt reporting, all AEs (expected or unexpected), all subject deaths, and all unexpected problems occurring during the reporting period should be described in the continuing review report submitted to the HQ USAMRMC IRB and should also be summarized in the final report at the conclusion of the study.

e. Findings and recommendations by the HQ USAMRMC IRB related to UPIRTSOs will be promptly reported to the CG, USAMRMC, the AHRPO and FDA, as required.

16-4. Deviations and Violations: Background

a. A deviation is an incident involving a departure from the IRB-approved protocol in the actual conduct of the study. Deviations may result from the action of the participant, investigator, or staff. Deviations include:

(1) Major deviations. Deviations are considered major when the unapproved change(s) in previously approved research activities, implemented without IRB approval, may potentially adversely affect subjects rights, safety, welfare, willingness to continue participation, or affect

the scientific design of the study and/or the integrity of the resultant data. Major deviations should be promptly reported to the HQ USAMRMC IRB.

(2) Minor deviations. Deviations are considered minor when the unapproved change(s) in previously approved research activities, implemented without IRB approval, do not adversely affect subjects or the integrity of the study data. Minor deviations should be reported to the HQ USAMRMC IRB at the time of continuing review.

(3) Violations. An incident involving an intentional deviation from the IRB-approved protocol that was not implemented in response to an emergency situation and that may impact a subject's rights, safety, and/or welfare, makes a substantial alteration to risks to subjects, or affects the scientific design of the study and/or the integrity of the resultant data. Violations may also be repeated deviations (major or minor) of the same nature. Violations can represent serious or continuing non-compliance with the federal regulations and guidelines for ethical conduct of human subject research.

(4) Protocol Exceptions. A protocol exception is an IRB-approved deviation for a single subject or a small group of subjects, but is not a permanent revision to the research protocol. Similar to an amendment, a protocol exception must be approved by the HQ USAMRMC IRB prior to its implementation (See Section 15-1).

16-5. Reporting Requirements for Major Deviations and Violations

a. Deviations that meet the definition of a major deviation, and all protocol violations, must be reported to the HQ USAMRMC IRB promptly following the Investigator's knowledge of the event, no matter how the deviation or violation was discovered (e.g. discovered by the sponsor during a monitoring visit, discovered by the Principal Investigator, etc.).

b. The Principal Investigator must submit to the HQ USAMRMC IRB a report that includes a description of the major protocol deviation(s), the plan to mitigate its negative effects, if any, and the plan to minimize or eliminate future occurrences. Examples of major deviations include, but are not limited to:

(1) Failure to obtain or document informed consent prior to any study-specific tests/procedures;

(2) Failure to perform a required lab test that, in the opinion of the principal investigator may affect subject safety or data integrity;

(3) Recurrence of minor deviations.

c. Emergency situations that required changes necessary to eliminate or reduce an apparent immediate harm or hazard for subjects (e.g., immediate reduction in the study drug dose due to new safety information or serious side effects) must be promptly reported to the HQ USAMRMC IRB following the Investigator's knowledge of the deviation. Implementing changes to protect subjects involved in research is always a higher priority than securing prior IRB approval. However, such changes must be reviewed by the HQ USAMRMC IRB promptly following their occurrence.

d. If the deviation involved an emergency administration or use of an FDA-regulated test article, the Principal Investigator must report to the IRB within *five* working days (21 CFR 50.23 and 56.104).

e. The HQ USAMRMC IRB Chair, Vice Chair or IRB member designee can review the deviation or violation report and remediation plan or refer the report for review by the convened IRB.

f. The convened HQ USAMRMC IRB or the Chair, Vice Chair or IRB member designee can accept the deviation report and remediation plan without modification. Alternatively, the convened IRB, or the IRB Chair or designee, can require changes to the remediation plan. The protocol may be suspended until the IRB's requirements have been implemented.

g. If it is necessary to make a permanent change to the study procedures in order to avoid harm to other subjects, then an amendment to the protocol must be submitted as soon as possible. If appropriate to maintain safety of the subjects, new subject enrollment should be temporarily stopped by the investigator until the amendment is approved.

16-6. Reporting Requirements for Minor Deviations

a. Deviations that meet the definition of a minor deviation, and that are not reoccurring, should be reported to the HQ USAMRMC IRB at the time of continuing review. Minor deviations should be described in summary form with sufficient detail so that the deviation is understandable. Any major deviations that occurred during the same approval period should be included in this summary for completeness. Examples of minor deviations may include, but are not limited to:

(1) Blood samples obtained at times close to but not precisely at the time points specified in the protocol;

(2) Routine safety lab work for a subject who has a history of previously normal lab values was either missed or was performed outside the protocol-defined window, but did not introduce any new safety concerns for the subject;

(3) Visit outside of study window but has no impact on the subject or study;

(4) Study procedure conducted out of sequence.

16-7. Reporting Requirement for Notification of Planned Inspections of Research by an Outside Governmental Agencies

As soon as a Principal Investigator learns of a planned compliance inspection, site visit, or audit of his/her study by another government agency, e.g., AHRPO, FDA, OHRP, etc., s/he should immediately inform the ORP IRB Office by telephone (DSN 343-2165 or 301-619-2165)

Chapter 17. Compliance Monitoring and Oversight Activities

Protection of human subjects in research starts with a written institutional commitment (i.e., a DOD Assurance for the Protection of Human Research Subjects or a Federalwide Assurance), promulgation of institutional policies and guidelines, and education on the IRB's written policies and procedures. In addition to these mandates, a proactive human research protection program is necessary to ensure compliance with the regulatory requirements of DOD and its components and to identify and prevent any unapproved protocol actions or deviations.

Initial review (Chapter 6) and continuing review through life cycle reporting (See Chapters 15 and 16) are the primary mechanisms by which the IRB monitors research. This chapter describes additional means by which the HQ USAMRMC IRB fulfills its oversight and monitoring responsibilities.

17-1. Medical Monitors

DODD 3216.02 requires that for research funded by the DOD involving more than minimal risk to subjects, an independent medical monitor must be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses, or other health care providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate. Depending on the nature of the study, the medical monitor may be assigned to assess one or more of the following phases of a research project: subject recruitment, subject enrollment, data collection, or data storage and analysis. At the discretion of the IRB, the medical monitor may be assigned to discuss research progress with the Principal Investigator, interview subjects, consult on individual cases, or evaluate AE reports. Medical monitors shall promptly report discrepancies or problems to the HQ USAMRMC IRB. They shall have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the medical monitor's report (DODD 3216.02, Paragraph 4.4.3.).

17-2. Data Monitoring Committees (DMC)

a. A DMC is a group of individuals with pertinent expertise that reviews on a regular basis accumulating data from an ongoing research protocol. All clinical trials and many other types of human research protocols require safety monitoring, but not all trials require a DMC. The HQ USAMRMC IRB may stipulate the requirement for a DMC when it finds that a DMC is needed to provide objective safety monitoring for a particular clinical trial or other protocol. This decision will be based on the size, scope, and risks of the study. In general, Phase III studies, large clinical trials, and studies presenting unusual risks to patients most often require review by a DMC. A DMC should also be established in trials where mortality and morbidity serve as the end points. The DMC is responsible for recommending trial termination when subject safety is jeopardized.

b. When a clinical trial or other protocol is determined by the HQ USAMRMC IRB to require a DMC, the DMC will be charged with reviewing and monitoring the accumulating data from an ongoing clinical trial on a regular basis. The Principal Investigator must submit as part of the protocol submission to the HQ USAMRMC IRB a copy of the DMC charter and a plan to assure regular submission of DMC reports to the IRB. After an appropriate analysis of the accumulated

data, the DMC should advise the Sponsor and the HQ USAMRMC IRB regarding the continuing safety of the subjects in the trial as well as the continuing validity of research. The DMC should report any early evidence of benefit or harm to trial participants that may be attributable to one of the treatments under evaluation. DMCs conduct the following activities as appropriate:

(1) Monitor and evaluate safety of the subjects as pre-specified in the interim monitoring plan of a protocol and adhere to all appropriate human subject protection requirements.

(2) Monitor and evaluate the efficacy of the treatments being tested as specified in the interim monitoring plan of a protocol.

(3) Monitor for early-unanticipated therapeutic results.

(4) Monitor the performance of the clinical trial.

(5) Make recommendations to the Sponsor and the HQ USAMRMC IRB to continue, amend, improve, terminate the study, plan additional and future clinical trials, recommend administrative adjustments, assess the appropriateness of the statistical assumptions, provide advice on an *ad hoc* basis to the Sponsor and the IRB for monitoring ongoing protocols, and ensure and preserve clinical trial integrity based on the interim analysis for safety and efficacy.

(6) Review safety data on a regular basis during the study and provide a written opinion to the Sponsor and the HQ USAMRMC IRB. The opinion will include:

(a) Risk assessment: Are study patients being exposed to unreasonable risk?

(b) Study continuation assessment: Does the DMC support continuation of the study without changes to the protocol? Does the DMC support continuation of the study but with specific changes to the protocol? Overall safety assessment (upon completion of the study).

c. At any point during the conduct of the study should the DMC observe a clinically significant unexpected difference in the safety profile emerging between the treatment group and control/comparison group or a greater than expected incidence of major complications in the entire study population, the DMC may (1) request that enrollment be suspended while the safety of subjects is further evaluated, (2) recommend stopping the study, or (3) recommend a change in the study for safety reasons. The final decision on the outcome of the DMC finding will be the responsibility of the Sponsor.

d. On the basis of information provided, the DMC has the mandate to recommend that the study be halted if there is strongly suggestive evidence of subject risk or treatment harm.

e. The DMC has the responsibility to request that enrollment be suspended at any time while a further evaluation of safety is undertaken.

17-3. Verification of Unapproved Changes in Approved Protocols

a. 32 CFR 219.103((4)(ii) requires written procedures which the IRB will follow for determining which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; this is a part of the HQ USAMRMC IRB's monitoring and oversight activities. The HQ USAMRMC IRB may consider the following in making determinations of which projects require this type of verification:

- (1) Randomly selected studies.
 - (2) Complex studies involving unusual levels or types of risk to subjects.
 - (3) Protocols conducted by investigators who previously may have failed to fully comply with the requirements of the regulations or the requirements of the HQ USAMRMC IRB.
 - (4) Protocols where concern about possible material changes occurring without IRB approval has been raised, based upon information provided in continuing review reports, or from other sources.
 - (5) Studies involving investigators with potential conflicts of interest, such as owning a significant amount of stock of the firm that is manufacturing the test agent.
 - (6) Protocols where issues have been raised by the medical monitor or by a DMC regarding any discrepancies observed, the medical condition of the subjects, or other matters that raise safety or other concerns.
- b. Need for an independent verification may be raised during a scheduled continuing review, review of safety or other updates, and at or in advance of any scheduled meeting. The HQ USAMRMC IRB Chair will determine if new reports and relevant IRB documents are immediately available or will have to be assembled for consideration at the next scheduled meeting. When advance notice is made, ORP IRB Office staff will review the appropriate information and prepare a focused review summary for consideration.
- c. If an indication exists that there may be a need for verification of study information by sources other than the investigators and that no material changes have occurred since the previous IRB meeting, the assigned HSPS will refer the protocol to the HQ USAMRMC IRB Chair or designee for further evaluation by the IRB.
- d. HQ USAMRMC IRB actions that may be considered include a finding of: (a) no verification needed; (b) examination of possible prior events through “For Cause” (FC) audit (see below) ; or (c) verification at specified intervals during the subsequent approval period.
- e. If, as a result of verification efforts by the HQ USAMRMC IRB, unapproved significant changes are found to have been deliberately instituted, the IRB will pursue the matter as a case of non-compliance with the federal requirements(See Chapter 18) and may require immediate suspension of IRB approval as a first step (See Chapter 19).

17-4. “For Cause” Study Audits to Assess Compliance

a. FC study audits to assess compliance are usually based on “red flags.” Examples of “red flags” include but are not limited to reporting of a high frequency of protocol deviations, investigators who repeatedly miss deadlines, or investigators who submit poor quality documents. Issues can be identified through review of the protocol or protocol life cycle actions, through information obtained on similar studies or studies conducted by the same Principal Investigator and through reporting of concerns to the IRB. A FC audit may stand alone or be initiated as part of an investigation into allegations of non-compliance.

b. A FC review by the ORP IRB Office may include: review of study master file documents; review of subject file documents, assessment of record management; focused review of consent form documentation; assessment of subject eligibility; assessment of source documentation; assessment of adherence to the approved protocol; review of test article accountability; observation of the informed consent process or study procedures; interviews with investigators and study staff.

c. At the end of the visit, the findings of the audit team, with any required corrective actions, will be provided to the Principal Investigator, the Institutional Official or his/her representative and other parties as appropriate.

d. If the audit raises urgent safety or regulatory concerns, the HQ USAMRMC IRB will be notified immediately to determine if a hold on new enrollment or study suspension is warranted pending further review of the audit report. Otherwise, the HQ USAMRMC IRB will be informed of any findings and any required corrective actions at the subsequent IRB meeting.

e. Upon review of the audit report, the HQ USAMRMC IRB may determine that additional actions are necessary. These actions could include but are not limited to termination or suspension of the research, training for the Principal Investigator and study personnel, or further investigation and consideration regarding serious and/or continuing non-compliance (see Chapter 18.)

Chapter 18. Serious or Continuing Non-Compliance

18-1. Investigating Allegations of Non-compliance

a. Instances of non-compliance should be reported to the HQ USAMRMC IRB. Allegations of non-compliance may be received by the IRB from a variety of sources, such as an Investigator, a research participant or their family members, institutional personnel, the Medical Monitor, IRB members, the media, or anonymous sources.

b. Allegations of non-compliance will be documented in as much detail as possible. This documentation will serve as the basis for subsequent investigation to validate or refute the allegation.

c. Allegations of non-compliance will be reported to the Institutional Official and investigated by the HQ USAMRMC IRB. The IRB may delegate the investigation to a subcommittee, an experienced IRB member, an experienced ORP IRB Office staff person, or other qualified individual(s) based on the nature and substance of the allegation or expertise required during the investigation. Consultants may also be involved in an investigation as appropriate.

d. Alleged non-compliance that may involve risks to subjects or others must be immediately investigated and actions taken to eliminate or minimize risk. Such allegations may involve:

(1) Actions or omissions that adversely affect the rights, safety, or welfare of participants;

(2) Actions or omissions that cause harm to participants or place participants at increased risk of harm;

(3) Actions that require legal or administrative action by the Command or otherwise directly involves the Command.

e. The investigation of non-compliance allegations will be conducted in a manner that is timely, thorough and impartial. To the extent possible, the investigation will be documented. Investigators will have the opportunity to provide input during the investigation and to provide relevant facts to the HQ USAMRMC IRB. Every effort will be made to protect the identity of whistle blowers during and after the investigation.

18-2. Determining Non-compliance

a. If the investigation substantiates the allegation of non-compliance, or if other instances of non-compliance are identified, the investigation results will be reported to the convened HQ USAMRMC IRB. The report will contain at a minimum a detailed description of the allegations, investigation findings, and recommendations for IRB findings that may include determinations of non-compliance, serious non-compliance, and/or continuing non-compliance.

b. Only the convened HQ USAMRMC IRB can make a determination of non-compliance. The convened IRB will review the results of the investigation and recommendations. The IRB will:

(1) Accept or reject the investigation result. If the IRB determines the investigation was not adequate, it may require additional investigation before making a determination regarding non-compliance.

(2) Accept or reject the determination of non-compliance. If the HQ USAMRMC IRB finds there is non-compliance, the IRB will determine if the non-compliance is serious and/or continuing.

(3) Identify actions to take to address the non-compliance (e.g., educate the investigator, educate all research staff, suspend/terminate the protocol, suspend/sanction the investigator, embargo data and /or publications, conduct random audits of the investigator or all investigators, etc.). The HQ USAMRMC IRB will take into account the situation and identify actions that are appropriate given the seriousness and magnitude of the non-compliance.

(4) Make recommendations to the appropriate Institutional Official regarding possible courses of action and corrective actions to address the non-compliance.

18-3. Documentation of Non-compliance

a. The HQ USAMRMC IRB minutes will reflect the determination of the IRB with regard to non-compliance. All remediation requirements will be documented in IRB minutes and provided to Investigators as stipulated actions.

b. The IRB or ORP IRB Office staff must document that remediation actions have been completed in a satisfactory manner and timeframe.

18-4. Reporting Requirements

a. 32 CFR 219.103(b)(5) requires “written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the department or agency head...of any serious or continuing noncompliance with this policy or the requirements or determinations of the IRB...”

b. Findings of serious or continued noncompliance with the regulatory requirements at 32 CFR 219, the applicable federal Assurance for the Protection of Human Research Subjects, institutional policies and procedures, or with the requirements or determinations of the HQ USAMRMC IRB shall be reported to the CG, USAMRMC and AHRPO as soon as possible after determination by the HQ USAMRMC IRB. The ORP IRB Office will formally notify the Principal Investigator and his/her Institutional Official of any findings or recommendations dealing with non-compliance. If the research involves an IND or Investigational Device Exemption (IDE) or if the funds supporting the research come from another federal department or agency, the appropriate officials at FDA, OHRP (if HHS sponsorship is also involved), etc., shall also be notified by the ORP IRB Office at the same time.

18-5. Appeal Process

a. Principal Investigators may appeal the HQ USAMRMC IRB’s findings of non-compliance, in writing, documenting the reasons for the appeal (within 30 days of being notified of the IRB’s decision).

b. Principal Investigators shall provide the written appeal along with any supporting documents through their Institutional Official to the HQ USAMRMC IRB Chair. The Chair will

review the appeal and decide if additional information is necessary prior to consideration at an IRB meeting. The appeal will be presented at a convened meeting of the HQ USAMRMC IRB, and the Principal Investigator will be invited to attend the meeting to address issues surrounding the appeal. Written notification of the HQ USAMRMC IRB's decision regarding the appeal will be sent to the Principal Investigator and his/her Institutional Official following the meeting.

c. The Principal Investigator is bound by the IRB's decision prior to and during an appeal.

d. Further Appeal. If a Principal Investigator disputes a determination of the HQ USAMRMC IRB, the Investigator may further appeal to his/her Institutional Official. The Institutional Official may use his/her discretion to determine the process for the appeal and grant or deny the appeal, including:

(1) Notifying the IRB of the appeal and requesting a response and relevant information from its records before making a decision;

(2) Submitting the appeal to mediation if the Investigator agrees to participate;

(3) Appointing a fact-finder to review the matter and report back;

(4) Seeking assistance from consultants or the Staff Judge Advocate of HQ USAMRMC or military or civilian attorney within the Office of the Staff Judge Advocate;

(5) Requesting the IRB consider other factors, information, or actions in relation to the decision under appeal.

e. Neither the Principal Investigator's Institutional Official nor any HQ USAMRMC official or committee may overturn the HQ USAMRMC IRB findings of non-compliance, nor exert undue pressure on the HQ USAMRMC IRB to reverse a decision.

f. Appeals of the Institutional Official's decision may be referred to the AHRPO for review.

Chapter 19. Suspension or Termination of IRB Approval

a. An IRB is required to suspend or terminate approval of research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action and shall be reported promptly to the Principal Investigator, appropriate institutional officials, and the department or agency head (32 CFR 219.113).

b. Any suspension or termination of the HQ USAMRMC IRB's approval of a study by the CG, USAMRMC shall be communicated by the ORP IRB Office to the Principal Investigator and his/her Institutional Official, and to the AHRPO. If the research involves an IND or IDE or the funds supporting the research come from another federal department or agency, the appropriate officials at FDA and/or OHRP (if HHS sponsorship is also involved), etc., shall also be notified by ORP IRB Office at the same time.

Chapter 20. Reporting the HQ USAMRMC IRB's Findings and Actions

32 CFR 219.103(4)(i) requires written procedures that the IRB will follow for reporting its findings and actions to the investigator and the institution.

20-1. Notification of Actions Based on the HQ USAMRMC IRB's Recommendations

The final determination made by the HQ USAMRMC IRB regarding a protocol, e.g., approval, conditional approval, deferral, or disapproval will be communicated in writing in a timely fashion to the Principal Investigator and his/her Institutional Official. The written notification will contain the HQ USAMRMC IRB's determination with accompanying stipulations and recommendations. If stipulations require submission of revisions to the protocol and/or consent form, such revisions should be submitted to the ORP IRB Office as soon as possible.

20-2. Notifications Regarding UPIRTSOs in a Study

Any findings by the HQ USAMRMC IRB based on the review of UPIRTSOs (See Chapter 16) in a study shall be promptly reported to the Institutional Official of the performance site, CG, USAMRMC, and the Director, AHRPO (who will report to the Director of Defense Research and Engineering), as required. In HHS sponsored or FDA regulated research, the appropriate institutional officials and the appropriate department or agency head (OHRP or FDA) shall be similarly notified promptly of any UPIRTSOs.

20-3. Notification Regarding Non-Compliance With Requirements

Regarding matters of findings of non-compliance with the regulatory requirements of DOD or its components, USAMRMC's formal notification of the Principal Investigator and his/her Institutional Official, the CG, USAMRMC, and the AHRPO shall be accomplished by the ORP IRB Office in a timely manner. If the research involves an IND or IDE or if the funds supporting the research come from another federal department or agency, the appropriate officials at FDA or OHRP shall also be notified at the same time. (Also refer to Chapter 18 of this document.)

Chapter 21. HQ USAMRMC IRB Records

32 CFR 219 and 21 CFR 50 and 56 require that an IRB prepares and maintains written procedures for and records of its operations and activities. This set of written policies and procedures have been adopted to govern the HQ USAMRMC IRB's operations and activities in accordance with 32 CFR 219.103 (b)(4) and (5).

21-1. IRB Protocol Master Files

Files are maintained for all human subjects protocols reviewed by the HQ USAMRMC IRB. These files include the following documents as appropriate/applicable:

- a. Tracking documents (e.g., Protocol Information Sheets, routing forms).
- b. General correspondence (e.g., protocol-related correspondence between the IRB and the investigator(s), emails, letters, telephone call records).
- c. Official correspondence (e.g., formal protocol-related correspondence between the IRB and the investigator(s)).
- d. HQ USAMRMC IRB official letters/memos (e.g., IRB official meeting outcome letter, IRB approval memo).
- e. Protocol reviews (e.g., consultant reports, reviewer check-lists, Memoranda for the Record (MFRs), response to recommendations, MFR requesting final documentation or approval, DSMB or DMC reports).
- f. Additional local IRB documentation (e.g., for OCONUS protocols).
- g. Protocol (initial submission and all subsequent approved versions).
- h. Consent form (initial submission and all subsequent approved versions).
- i. Study instruments (e.g., questionnaires, case report forms, recruitment material).
- j. Scientific review documentation.
- k. HQ USAMRMC IRB read-ahead packets (includes items related to full IRB review of a protocol).
- l. Proposal.
- m. CVs/biographical sketches, human subjects protection training documentation, COI statements for Principal Investigator and key study personnel.
- n. Investigator's Brochure/device manual/product information and FDA forms and communications (as appropriate).
- o. Documentation related to continuing review.
- p. Amendments.

- q. Adverse event reports, Medical Monitor reports.
- r. Deviations reports.
- s. Any statements of significant new findings to be provided to subjects.
- t. Other related documents as appropriate.
- u. Final study reports.
- v. Award documents.

21-2. Files on Studies Determined to be Not Research, Not Human Subjects Research, or Exempt Human Subjects Research

Files of project materials are maintained for activities determined to not meet the definition of research or the definition of human subjects IAW 32 CFR 219.102, or determined to be exempt under one or more categories at 32 CFR 219.101(b), including documentation of the basis for the finding and the applicable exemption number.

21-3. IRB Membership Roster

A list of the IRB's primary members and alternates identified by name, earned degrees, representative capacity (identifying the corresponding primary member in whose place an alternate may serve), expertise such as board certifications, licenses, or other relevant experience showing each member's area of contribution to IRB deliberations, and any employment or other relationship between each member and DOD are maintained. Whenever the membership of the IRB changes, a new dated roster is produced.

21-4. Minutes of HQ USAMRMC IRB Meetings

The minutes of HQ USAMRMC IRB meetings will document the presence of a quorum, the time period the meeting is convened and adjourned, recusals due to conflict of interest, and separate deliberations, actions, and votes for each protocol undergoing initial or continuing review by the convened IRB. Reasons for votes of disapproval or abstention will be documented. The Common Rule (32 CFR 219.115) requires that the minutes of IRB meetings shall be recorded in sufficient detail to show:

- a. Attendance at the meetings. The list of attendees must include the names, earned degrees, professional expertise (including status as non-scientist), and institutional affiliations of the participating individuals. They may be categorized in the following manner: the primary members participating, the alternates participating on behalf of the primary members absent, and the primary members absent. This information may be presented in an IRB Membership tabular roster format.
- b. Actions taken by the HQ USAMRMC IRB.
- c. Vote on these actions including the number of members voting for, against, and abstaining.

- d. The basis for requiring changes in, deferring, or disapproving research.
- e. Written summary of the discussion of controverted issues and their resolution.

The minutes will also record the findings where the regulations of DOD or its components require specific findings on the part of IRB, such as:

- a. Approving research with waiver of informed consent.
- b. Approving research with waiver of the documentation of informed consent.
- c. Approving research involving pregnant women or children.

The list of attendees will also include the names of all non-member persons attending any part of the IRB meeting and may list them as guests, if appropriate.

21-5. Other HQ USAMRMC IRB Correspondence

Other correspondence to or from the HQ USAMRMC IRB is retained. Examples of such correspondence include but are not limited to findings or recommendations on general issues to CG, USAMRMC; official communications with FDA, AHRPO, and other regulatory bodies; lists of protocols and protocol actions reviewed and approved by expedited review; and site visit reports and responses from the site regarding any findings.

21-6. Policy Memoranda

Original signed HQ USAMRMC IRB Policy Memoranda are maintained in the Office of the Director, ORP.

21-7. Security of Records

- a. All HQ USAMRMC IRB records will be kept securely in locked storage rooms, locked filing cabinets, or in restricted computer files.
- b. All records shall be accessible for inspection and copying by authorized representatives of the DOD or, as applicable, FDA at reasonable times and in a reasonable manner.
- c. In addition, other individuals and groups may legitimately obtain copies of particular documents or, exceptionally, have access to files. This may include investigators, representatives from the DOD, FDA and other federal agencies as determined by law and regulations, and private individuals requesting copies of HQ USAMRMC IRB minutes under applicable Freedom of Information Act laws. If rights of access are at all unclear, the Director, ORP, will consult with the SJA of USAMRMC.

21-8. Records Retention

The records required by this policy will be retained for at least three years after completion of the research (32 CFR 219.115). Records related to FDA regulated studies will be retained on site in central files until two years after approval of the investigational product or two years after discontinuation or withdrawal of the IND and notification of the FDA (see 21 CFR 312.64).

Chapter 22. Quality Assurance (QA)

Assuring high quality performance by taking steps that assure and enhance protections for the rights and welfare of the human research subjects beyond the minimal regulatory requirements, and preventing, finding, and overcoming episodes of non-compliance are among the specific minimal objectives of the ORP IRB Office's QA activities. The QA activities include:

a. Education and Training. All IRB members and ORP IRB Office HSPSs receive training on the Belmont Principles, the Nuremberg Code, 32 CFR 219, DOD and Army human subjects protection regulations, and the IRB policies and procedures. Board members and IRB Office staff are provided with hard copy regulatory reference materials to assist them in their reviews of protocols. Board members and IRB Office staff are funded to attend the Public Responsibility in Medicine and Research National IRB Conference on a biannual basis. The Director, ORP forwards information to IRB members and staff on current topics in human subjects protection on an ongoing basis, and hard copy educational materials are included in each IRB read-ahead packet.

b. HSPSs conduct protocol pre-reviews using standardized regulatory checklists to ensure protocols receive consistent, comprehensive, and complete reviews. HSPSs' reviews are then reviewed for completeness and accuracy by senior ORP IRB Office or ORP HRPO staff members.

c. HQ USAMRMC IRB members conduct expedited reviews using standardized regulatory checklists to ensure that all criteria for approval are satisfied.

d. OTSG Consultants and subject matter experts are available to assist the IRB in evaluating the scientific and/or ethical issues of protocols for which the Board may not have expertise.

e. HQ USAMRMC IRB policies and procedures are periodically reviewed to ensure relevancy and consistency.

f. Each month, an ORP IRB Office staff member reviews the OHRP determination letters and FDA warning letters and distributes this information to the HQ USAMRMC IRB members and HSPSs for consideration in their review of protocols.

g. Customized reports are routinely used to evaluate the status reflected in the ORP Information Management System tracking database for HQ USAMRMC IRB protocols, e.g., approval status, continuing review expiration date.

h. A percent of HQ USAMRMC IRB protocol master files are assessed each month for completeness using standardized checklists.

i. The HQ USAMRMC IRB may select one or more protocols per month or per quarter for a QA audit, depending upon the available resources. A QA audit may consist of a limited desk audit through request of current materials or an on-site visit to inspect study records. A QA audit by the ORP IRB Office may include: review of study master file documents; review of subject file documents, assessment of record management; focused review of consent form documentation; assessment of subject eligibility; assessment of source documentation; assessment of adherence to the approved protocol; review of test article accountability; observation of the consent process or study procedures; and interviews with investigators and

study staff. An important benefit of these interactions is the increased personal communication that may be achieved between the reviewers and those whose work is reviewed. A QA audit may also identify needed revisions in local policies and procedures or uncover the need for a more thorough FC audit to assess the extent of non-compliance (see Chapter 17)

j. The AHRPO conducts headquarters-level review of all HQ USAMRMC IRB protocols and conducts periodic site visits (see Chapter 23).

Chapter 23. AHRPO Headquarters-Level Administrative Review (HLAR) of HQ USAMRMC IRB Actions

a. Protocols and supporting documentation from the HQ, USAMRMC IRB's reviews of all protocol actions will be forwarded by the ORP IRB Office staff to AHRPO for HLAR following final IRB approval. Documentation from communications regarding any issues identified during the AHRPO HLAR and the AHRPO's HLAR concurrence with the HQ USAMRMC IRB's actions will be maintained in the IRB master file for the respective protocol.

b. The AHRPO receives and electronically archives the following protocol-related documents for HLAR compliance review:

(1) HQ USAMRMC IRB approval (or other action) memoranda.

(2) Protocol review documents and checklists.

(3) Protocol and consent forms.

(4) Investigators' and medical monitor's (as applicable) CVs and human subjects protection training certificates.

(5) Advertisements and other recruitment materials.

(6) Other documents as appropriate (e.g., Form FDA 1572, Investigator's Brochure, etc).

(7) Amendments.

(8) Continuing reviews.

(9) Reports of serious unexpected AEs and/or unanticipated problems.

(10) HQ USAMRMC IRB meeting minutes.

(11) Documentation of suspensions or terminations.

c. Additionally, the AHRPO will review and archive the following:

(1) HQ USAMRMC IRB written policies and procedures.

(2) HQ USAMRMC IRB membership rosters.

Appendix A. References to Ethical Principles, Federal Requirements, Guidelines

Nuremburg Code, 1946

Belmont Report, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, 18 April 1979

World Medical Association (WMA) Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects. 59th WMA General Assembly, Seoul, October 2008

Council for International Organizations of Medical Sciences - *International Ethical Guidelines for Biomedical Research Involving Human Subjects* (Council for Organizations of Medical Sciences (CIOMS) International Ethical Guidelines) Prepared by CIOMS in collaboration with the World Health Organization (WHO) 2002

International Conference on Harmonization (ICH) - Harmonized Tripartite Consolidated Guideline for Good Clinical Practice: Efficacy Guideline - 6 (ICH-GCP-E6)

10 United States Code (USC) 980, *Limitation on Use of Humans as Experimental Subjects*

10 United States Code 1107, *Notice of Use of an Investigational New Drug or a Drug Unapproved for Its Applied Use*, 18 Mar 2004

24 United States Code 30, *Payments to Donors of Blood for Persons Undergoing Treatment at Government Expense*, 1 June 2003

32 Code of Federal Regulations (CFR) 219, *Protection of Human Subjects*, 18 June 1991 (also called the Federal Policy or the Common Rule)

21 CFR 50, *Protection of Human Subjects*, 30 May 1980

21 CFR 54, *Financial Disclosure by Clinical Investigators*, 1 April 2003

21 CFR 56, *Institutional Review Boards*, 27 January 1981

21 CFR 312, *Investigational New Drug (IND) Application*, 4 January 1999

21 CFR 812, *Investigational Device Exemptions (IDEs)*, 4 January 2000

Defense Acquisition Regulations System 48 CFR Parts 207, 235, and 252
Defense Federal Acquisition Regulation Supplement; Protection of Human Subjects in Research Projects (DFARS Case 2007-D008)

Department of Defense Directive (DODD) 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research*, 25 March 2002

Department of Defense Instruction (DODI) 3210.7, *Research Integrity and Misconduct*, 14 May 2004

DODI 6200.02, *Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs*, February 27, 2008

Office of the Secretary of Defense Memorandum, *Department of Defense (DOD) Guidance for Assurance of Compliance with the Federal Policy for the Protection of Human Subjects*, 10 June 1993

Army Regulation (AR) 70-25, Use of Volunteers as Subjects of Research, 25 January 1990

AR 40-7, Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances, 19 October 2009

AR 40-38, Clinical Investigation Program, 1 September 1989

USAMRDC Reg 70-25 (20 April 1990)

USAMRMC Reg 70-25 (USAMRDC Reg 70-25 - as amended - July 2003)

The List of Categories of Research That May be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure; 63 Federal Register (FR) 60364 – 60367; 9 November 1998

Food and Drug Administration (FDA) Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators 1998, FDA

Office for Human Research Protections (OHRP) Compliance Activities: Common Findings and Guidance, 10 July 2002, OHRP

OHRP's Institutional Review Board Guidebook, 1993

Message, ALARACT 031/2008, *Army Human Subjects Protection Requirements* DTG 141557Z Feb 08

Department of Health and Human Services Final Guidance Document, *Financial Relationships and Interests in Research Involving Human Subjects: Guidance for Human Subject Protection*, May 5, 2004

Memorandum from the Director, Division of Human Subject Protections, OPRR, *IRB Knowledge of Local Research Context*, August 27, 1998, updated July 21, 2000

The University of Miami's Collaborative Training Initiative (CITI) HQ USAMRMC IRB Online Tutorial Module 11: *Internet Research*

OHRP: *Issues to Consider in the Research Use of Stored Data or Tissues*, November 1997

OHRP: *Guidance on Research Involving Coded Private Information or Biological Specimens*, August 10, 2004

Ethical Principles

Protections for human research subjects are primarily founded on the three basic principles of the Belmont Report (1979). These principles are: (1) respect for persons; (2) beneficence; and (3) justice. These fundamental principles for the protection of human research subjects are

embodied in the federal regulations at 32 CFR 219, also called the Federal Policy or the Common Rule. The HQ USAMRMC IRB's written operational policies and procedures are based primarily on the requirement of these federal regulations and also other requirements.

Human subjects research at performance sites in foreign countries may be conducted by procedures normally followed in those countries and is based on principles such as those of the Declaration of Helsinki (2000) or the International Ethical Guidelines for Biomedical Research Involving Human Subjects (2002) (ICH-GCP-E6), provided the procedures prescribed by the foreign institution afford protections that are at least equivalent to those provided in the Common Rule (see 32 CFR 219.101(h)).

Laws, Regulations, Directives, and Instructions

The HQ USAMRMC IRB operates under the following statutory laws, federal regulations, DODD, DODI, DA regulations, and USAMRMC Policies:

Statutory Laws

10 USC 980 (last amended 2002) – *Limitation on use of humans in research*. This law states that the funds appropriated to the DOD may not be used for research involving a human being as an experimental subject unless –

- a. the informed consent of the subject is obtained in advance; or
- b. in the case of research intended to be beneficial to the subject, the informed consent of the subject or a legal representative of the subject is obtained in advance.

This second clause of 10 USC 980 requires that in case a subject is incapable of providing informed consent, the informed consent in advance may alternatively be obtained from a legal representative of the subject, provided it is shown that participation in the research is intended to be beneficial to the individual subject.

Thus, if an investigator plans to enroll subjects who are not capable of providing their own informed consent, the investigator needs to demonstrate a clear intent to benefit each subject participating in the study.

This “intent to benefit” requirement often makes placebo-controlled clinical trials enrolling incapacitated individuals, incompetents, or minors problematic. Investigators must be able to articulate how their research intends to benefit individual subjects if the participants will be enrolled in the placebo arm of the trial. For example, a subject in the placebo arm may benefit directly from medical treatment or increased surveillance provided as a consequence of participation in the research that is beyond the standard of care.

Because both clauses mandate advance informed consent, 10 USC 980 has historically prevented the DOD from funding emergency research in which advance informed consent of subjects cannot be obtained (e.g., research involving new treatments for trauma victims), even if such research would otherwise have been in compliance with all other applicable laws.

The National Defense Authorization Act of 2002 amended 10 USC 980 to address this issue. The amendment permits the Secretary of Defense to waive the requirement for advance informed consent “with respect to a specific research project to advance the development of a

medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws.” In DODD 3216.02, the Secretary of Defense delegated this waiver authority to the Heads of DOD Components (e.g., Secretary of the Army).

In 2004, DOD General Counsel provided guidance on the applicability of 10 USC 980 to human subject research. This legal opinion states that 10 USC 980 applies only when the research or clinical investigation involves an intervention or an interaction in which the primary purpose of the intervention or interaction is to obtain data about the effects of the intervention or interaction on the individual. The HQ USAMRMC IRB relies on this legal opinion to determine the applicability to 10 USC 980.

The “other applicable laws” relevant to this research are the FDA regulation at 21 CFR 50.24, Exception from Informed Consent Requirements for Emergency Research, or the harmonized U.S. Department of Health and Human Services (HHS) regulations.

10 USC 1107 (as released on 18 March 2004): For details, see Chapter 14.

Federal Regulations

32 CFR 219: *Protection of Human Subjects* (the Common Rule).

45 CFR 46: Subpart B: *Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization*; Subpart C: *Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects*; and Subpart D: *Additional Protections for Children involved as Subjects in Research*

21 CFR 50: Protection of Human Subjects (FDA)

21CFR 54: Financial Disclosures by Clinical Investigators (FDA)

21 CFR 56: Institutional Review Boards (FDA)

21 CFR 312: Investigational New Drug (IND) Application (FDA)

21 CFR 812: Investigational Device Exemption (IDE) (FDA)

45 CFR 160 & 164: Health Insurance Portability and Accountability Act (HIPAA) of 1996 (<http://www.hhs.gov/ocr/hipaa/>)

DOD Directive (DODD)

DODD 3216.02: *Protection of Human Subjects and Adherence to Ethical Standards in DOD-Supported Research*. This directive establishes the ethical conduct of investigators for both intramural and extramural research and protects the rights and welfare of humans as subjects of study in DOD-supported RDT&E and other related activities hereafter referred to as “research.”

DOD Instructions (DODI)

DODI 6200.02: *Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs*. This Instruction describes responsibilities for

implementation of 10 United States Code (USC) 1107 (Notice of Use of an Investigational New Drug or a Drug Unapproved for its Applied Use) and prescribes the process for review and approval of DOD contingency IND protocols for FHP. The DOD FHP program is an organized program of healthcare preventive or therapeutic treatment, or preparations for such treatment, designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions. Within DODI 6200.02, the HQ USAMRMC IRB (formerly known as the Human Subjects Research Review Board or HSRRB) is designated as the IRB of Record for review and approval of the DOD contingency IND protocols for FHP. These protocols undergo initial and continuing IRB review and approval, and are available to be implemented when needed.

DODI 3210.7: *Research Integrity and Misconduct*. This Instruction supplements the policy established by paragraph 4.8. of DODD 3216.02 and implements subparagraph 5.1.5 of DODD 3216.02 by specifying detailed procedures and standards for the DOD for the prevention of research misconduct. This Instruction is consistent with the "Federal Policy on Research Misconduct" which calls upon those federal agencies that support or conduct research on an intramural or extramural basis to issue policies and procedures that conform to the federal Policy.

Department of the Army (DA) Regulations

Army Regulation (AR) 70-25: *Use of Volunteers as Subjects of Research*. This regulation refers to research conducted by DA, contractor, grantee, or other agency using U.S. Army funds. This includes biomedical research and behavioral studies involving human subjects; RDT&E activities involving new drugs, vaccines, biologics, or investigational medical devices; inclusion of human subjects as objects of research involving more than minimal risks in testing of weapons, vehicles, aircraft, and other materiel; research involving exposures of subjects to nuclear weapons effect, chemical warfare agents, or biological warfare agents; and activities funded by non-Army resources in which subjects are DA military or civilian personnel.

TSG is specifically designated to be the final approval authority of IRB recommendations for approval of human subjects research in the following categories:

- a. Studies involving human subjects using Schedule I controlled drug substances (AR 40-7).
- b. Research involving minors or other vulnerable categories of human subjects, when subjects are wards of a state or other agency or institution (AR 70-25 (2-5g)).
- c. Research proposals from Major Army Commands (MACOMs) that do not have a HUC or an internal review process (AR 70-25 (2-5d)).
- d. Research involving Army's health hazard assessment program and health hazards of medical and non-medical materiel.
- e. Direct medical follow up, when appropriate, on research subjects to ensure that any long-range problems are detected and treated.

AR 40-7, *Use of U.S. Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances*. This regulation prescribes DA policies, procedures, and responsibilities for the use of FDA-regulated investigational products, the use of FDA-approved drugs for unapproved indications in humans, and the use of U.S. Drug

Enforcement Administration Schedule I controlled substances in humans and animals where DA facilities, personnel, or financial support are used.

Appendix B. Definitions

Federal Definitions

Clinical Investigation - Any experiment that involves a test article and one or more human subjects and that is subject to the Food and Drug Administration regulations.

Test Article - Any drug (including a biological product for human use), medical device for human use, human food additive, color additive, electronic product, or any other article subject to FDA regulation.

Department or Agency Head - The head of any federal department or agency and any other officer or employee of any department or agency to whom authority has been delegated.

Institution - Any public or private entity or agency (including federal, state, and other agencies).

Legally Authorized Representative (also referred to as surrogate or proxy) - 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.

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

Research Subject to Regulation and similar terms are intended to encompass those research activities for which a federal department or agency has specific responsibility for regulating as a research activity (for example, Investigational New Drug requirements administered by the FDA). It does not include research activities which are incidentally regulated by a federal department or agency solely as part of the department's or agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, wage and hour requirements administered by the Department of Labor).

Human Subject - A living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual or identifiable private information. *Intervention* includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator associated with the information) in order for obtaining the information to constitute research involving human subjects. NOTE: The Food and Drug Administration (FDA) defines a *human subject* as an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient.

IRB - An Institutional Review Board established in accord with and for the purposes expressed in this policy.

IRB Approval - The determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and federal requirements.

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 or psychological examinations or tests.

Certification - The official notification by the institution to the supporting Department or Agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

Unanticipated Problems and Adverse Events Definitions

Unanticipated Problems Involving Risks to Subjects or Others (UPIRTSOs) - Any incident, experience, or outcome that meets all of the following criteria: unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; related or possibly related to a subject's participation in the research; and suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) related to the research than was previously known or recognized.

Associated With the Use of the Study Product (Drug or Device) or Procedure - Means there is a reasonable possibility that the experience may have been caused by the drug (21 CFR 312.32(a)).

Adverse Event/Experience (AE) - An AE is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can, therefore, be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product (ICH-GCP-E6).

Serious Adverse Drug Event/Experience (SAE) - Any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of an existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse (21 CFR 312.32(a)).

Life-threatening Adverse Drug Event/Experience - Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death (21 CFR 312.32(a)).

Unexpected Adverse Drug Experience - Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure, or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product" (21 CFR 312.32(a)).

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

45 CFR 46, Subpart B Definitions

Dead Fetus - A fetus that exhibits neither heartbeat, spontaneous respiratory activity, spontaneous movement of voluntary muscles, nor pulsation of the umbilical cord (if still attached).

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

Fetus - The product of conception from implantation until delivery.

Human Fetal Tissue - Tissue or cells obtained from a dead human embryo or fetus after a spontaneous or induced abortion, or after a stillbirth.

Neonate - A newborn.

Nonviable Neonate - A neonate after delivery that, although living, is not viable.

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

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

45 CFR 46, Subpart D Definitions

Assent - A child's affirmative agreement to participate in research obtained in conjunction with permission from the individual's parents or legally authorized representative. A failure of a subject to object should not be construed as assent, absent affirmative agreement.

Children/Minors - Persons who have not attained the legal age for consent to treatments or procedures involved in research, under the applicable law of the jurisdiction in which the research will be conducted.

Permission - The agreement of parent(s) or guardian(s) to the participation of their child or ward in research.

The HQ USAMRMC IRB's Working Definitions

Advertising - A public announcement usually by a printed notice or voice or data broadcast that describes a research study including contact information. Typically this is used for recruitment purposes for a research study.

Assent - An individual's affirmative agreement to participate in research obtained in conjunction with permission from the individual's parents or legally authorized representative. A failure of a subject to object should not be construed as assent, absent affirmative agreement.

Cadaver - a deceased person or portion thereof. The term cadaver includes organs, tissue, eyes, bones, arteries or other portion of a deceased person. The term cadaver does not include portions of an individual, such as tissue of blood, that were removed from the individual for research purposes while the individual was still alive.

Coded Information - Identifying information that would enable the investigator to readily ascertain the identity of the individual to whom the private information or specimens pertain has been replaced with a number, letter, symbol, or combination thereof and a key to decipher the code exists, enabling linkage of the identifying information to the private information or specimens.

Cognitive Impairment - An inability to reason, think, perceive, or remember. Cognitive impairment may result from progressive disease, injury, medication, or experience. Tests of cognitive ability carried out by qualified professionals are used to identify cognitive impairment.

Continuing non-compliance - A pattern of actions or omissions that suggest a likelihood that, without intervention, instances of non-compliance will recur, or that indicate an unwillingness to comply with, or a lack of knowledge of, federal and DOD regulations, policy, and law, or determinations or requirements of the IRB.

Dissent - An individual's negative expressions, verbal or non-verbal, that they object to participation in the research or research activities.

Force Health Protection (FHP) - An organized program of healthcare preventive or therapeutic treatment or preparations for such treatment designed to meet the actual, anticipated, or potential needs of a group of military personnel in relation to military missions (DODI 6200.02).

Health Care Agent - The health care agent is the individual named in a Durable Power of Attorney for Health Care order executed by the subject while the subject had decision-making capacity. The health care agent acts on the subject's behalf to make health care decisions, including enrolling the subject in a research study, when the subject is unable to provide consent.

Human Research Protection Program – A system of interdependent elements that come together to implement policies and practices that ensure the protection of research participants.

Informed Consent - An individual's voluntary agreement, based upon adequate knowledge and understanding of relevant information, to participate in research or to undergo a diagnostic, therapeutic, or preventive procedure.

IRB of Record - The IRB that assumes primary responsibility for review and oversight of a protocol.

Key Research Personnel - Persons listed on human research protocols who have direct contact with subjects or their records/data/identifiable specimens.

Legal Guardian or Conservator - A legal guardian or conservator is a person appointed by a court to make decisions for an individual who has been judicially determined to be incompetent.

Local IRB Review - Review conducted by the IRB of the institution where the research will be implemented.

Prospective Research - Research using humans as subjects or identifiable human specimens/data that will be collected after the research is approved by the IRB.

Quality Assurance (QA) - QA focuses on the quality of the processes contributing to the completion of a product or an activity. QA is a proactive effort with a goal to minimize the need for QC where quality is built into processes so that need to inspect afterward is minimized. It refers to every component, including personnel, of the institution that produces a particular product (e.g., a vaccine) or performs a given activity (e.g., performing IRB review or conducting informed consent process), meeting minimum (the "floor") requirements. In case of a clinical trial, QA refers to all those planned and systematic actions that are established to ensure that the trial is performed and the data are generated, documented and reported in compliance with good clinical practice (GCP) and the applicable regulatory requirements.

Recruitment - Seeking individuals to enroll or participate in a research project.

Research Not Involving Human Subjects - An activity that has been determined to meet the 32 CFR 219.102 definition of "research" but not meet the definition of "human subject."

Retrospective Research - Research using identifiable human specimens/data that were previously collected (i.e., on the shelf) before the research was submitted to the ORP IRB Office for review.

Serious non-compliance - An action or omission that adversely affects the rights, safety, or welfare of participants, placing participants at increased risk of harm, or causing harm to participants.

Short Form Consent - A written informed consent document that summarizes the required elements of informed consent to be presented orally to the participant or his or her legally authorized representative.

Appendix C. CITI Training Modules

Required CITI Modules for Investigators, Key Research Personnel, and Medical Monitors Conducting Biomedical Research

- (1) History & Ethical Principles
- (2) Defining Research With Humans – SBR (Social-Behavioral Research)
- (3) Basic IRB Regulations & Review Process
- (4) Assessing Risks – SBR
- (5) Informed Consent
- (6) Privacy and Confidentiality - SBR
- (7) SBR for Biomedical Researchers
- (8) Records-Based Research
- (9) Genetic Research in Human Populations
- (10) Research With Protected Populations – Overview
- (11) Internet Research – SBR
- (12) Group Harms - Research With Culturally or Medically Vulnerable Groups
- (13) FDA-Regulated Research
- (14) HIPAA and Human Subjects Research
- (15) Hot Topics
- (16) Conflicts of Interest

Required CITI Modules for Investigators, Key Research Personnel, and Medical Monitors Conducting Social-Behavioral Research

- (1) History and Ethics – SBR
- (2) Defining Research With Humans – SBR
- (3) The Regulations and SBR
- (4) Assessing Risks – SBR
- (5) Informed Consent - SBR
- (6) Privacy and Confidentiality – SBR
- (7) Records-Based Research
- (8) Research With Protected Populations – Overview

- (9) Internet Research – SBR
- (10) Group Harms - Research With Culturally or Medically Vulnerable Groups
- (11) HIPAA and Human Subject Research
- (12) Hot Topics
- (13) Conflicts of Interest

Additional Required CITI Modules for Investigators, Key Research Personnel, and Medical Monitors Conducting Research With Vulnerable Populations

- (1) Research With Prisoners – SBR
- (2) Vulnerable Subjects - Research With Prisoners
- (3) Research With Children – SBR
- (4) Vulnerable Subjects - Research Involving Minors
- (5) Research in Public Elementary and Secondary Schools – SBR
- (6) Vulnerable Subjects - Research Involving Pregnant Women and Fetuses in Utero
- (7) Workers as Research Subjects- A Vulnerable Population

Required CITI Modules For HQ USAMRMC IRB Members, Chair, Vice Chair, and Administrator

- (1) History and Ethical Principles
- (2) Defining Research With Human Subjects - SBR
- (3) The Regulations and the Social and Behavioral Sciences - SBR
- (4) Basic Institutional Review Board (IRB) Regulations and Review Process
- (5) Assessing Risk in Social and Behavioral Sciences - SBR
- (6) Informed Consent - SBR
- (7) Informed Consent
- (8) Privacy and Confidentiality - SBR
- (9) Social and Behavioral Research for Biomedical Researchers
- (10) Records-Based Research
- (11) Genetic Research in Human Populations
- (12) Research With Protected Populations - Vulnerable Subjects: An Overview

- (13) Research With Prisoners - SBR
- (14) Research With Children – SBR
- (15) Vulnerable Subjects - Research Involving Minors
- (16) Research in Public Elementary and Secondary Schools - SBR
- (17) Vulnerable Subjects - Research Involving Pregnant Women and Fetuses in Utero
- (18) International Research - SBR
- (19) Internet Research - SBR
- (20) Group Harms: Research With Culturally or Medically Vulnerable Groups
- (21) FDA-Regulated Research
- (22) Human Subjects Research at the VA
- (23) HIPAA and Human Subjects Research
- (24) Workers as Research Subjects - A Vulnerable Population
- (25) Hot Topics
- (26) Conflicts of Interest in Research Involving Human Subjects
- (27) The IRB Member Module - "What Every New IRB Member Needs to Know"

Required CITI Modules For Human Subjects Protection Scientists

- (1) History and Ethical Principles
- (2) Defining Research With Human Subjects - SBR
- (3) The Regulations and the Social and Behavioral Sciences - SBR
- (4) Basic Institutional Review Board (IRB) Regulations and Review Process
- (5) Assessing Risk in Social and Behavioral Sciences - SBR
- (6) Informed Consent - SBR
- (7) Informed Consent
- (8) Privacy and Confidentiality - SBR
- (9) Social and Behavioral Research for Biomedical Researchers
- (10) Records-Based Research
- (11) Genetic Research in Human Populations
- (12) Research With Protected Populations - Vulnerable Subjects: An Overview

- (13) Research With Prisoners - SBR
- (14) Research With Children – SBR
- (15) Vulnerable Subjects - Research Involving Minors
- (16) Research in Public Elementary and Secondary Schools - SBR
- (17) Vulnerable Subjects - Research Involving Pregnant Women and Fetuses in Utero
- (18) International Research - SBR
- (19) Internet Research - SBR
- (20) Group Harms: Research With Culturally or Medically Vulnerable Groups
- (21) FDA-Regulated Research
- (22) Human Subjects Research at the VA
- (23) HIPAA and Human Subjects Research
- (24) Workers as Research Subjects - A Vulnerable Population
- (25) Hot Topics
- (26) Conflicts of Interest in Research Involving Human Subjects

Glossary of Abbreviations

Abbreviation	Meaning
AE	Adverse Event
AHRPO	Army Human Research Protections Office
AMEDD	Army Medical Department
AR	Army Regulation
AS	Administrative Simplification
ASG, FP	Assistant Surgeon General, Force Projection
CFR	Code of Federal Regulations
CG	Commanding General
CIOMS	Council for Organizations of Medical Sciences
CITI	Collaborative Institutional Training Initiative
COI	Conflict of Interest
CV	Curriculum Vitae
DA	Department of the Army
DDR&E	Director of Defense Research and Engineering
DHHS	Department of Health and Human Services
DMC	Data Monitoring Committee
DOD	U.S. Department of Defense
DODD	Department of Defense Directive
DODI	Department of Defense Instruction
DMC	Data Monitoring Committee
DSMB	Data Safety Monitoring Board
EPHI	Electronic Protected Health Information
FC	For Cause
FDA	Food and Drug Administration
FHP	Force Health Protection
FOIA	Freedom of Information Act
FR	Federal Register
GTMR	Greater than Minimal Risk
HIPAA	Health Insurance Portability and Accountability Act
HLAR	Headquarters-Level Administrative Review
HPA	Human Protections Administrator
HQ	Headquarters
HRPO	Human Research Protection Office
HRPP	Human Research Protection Program
HSPS	Human Subjects Protection Scientist
IAW	In Accordance With
ICH-GCP-E6	International Conference on Harmonization – Good Clinical Practice – Efficacy Guideline 6
IDE	Investigational Device Exemption
IMS	Information Management System
IND	Investigational New Drug
IP	Internet Protocol
IPA	Intergovernmental Personnel Act
IRB	Institutional Review Board
IRB Office	Institutional Review Board Office

LAR	Legally Authorized Representative
MEDCOM	Medical Command
MFR	Memorandum for Record
MTF	Military Treatment Facility
NCO	Noncommissioned Officer
NGTMR	No Greater Than Minimal Risk
NIH	National Institutes of Health
OCONUS	Outside Continental United States
OHRP	Office for Human Research Protections
ORP	Office of Research Protections
OTSG	Office of the Surgeon General
PHI	Protected Health Information
PRIM&R	Public Responsibility in Medicine and Research
QA	Quality Assurance
RDT&E	Research, Development, Test & Evaluation
RHI	Research Health Information
SAE	Serious Adverse Event
SJA	Staff Judge Advocate
TSG	The Surgeon General
UPIRTSO	Unanticipated Problem Involving Risks to Subjects or Others
URL	Universal Resource Locator
USAMRMC	United States Army Medical Research and Materiel Command
USC	United States Code
USCENTCOM	United States Central Command
VA	Veterans Affairs
VRMS	Volunteer Registry Management System
WHO	World Health Organization