Defense Health Agency
Headquarters,
Medical Research and Development Command
(HQ MRDC)

Office of Human and Animal Research
Institutional Review Board Office

HQ MRDC Institutional Review Board
Policies and Procedures
Reflecting 2018 Common Rule Requirements

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Chapter 1. Introduction

1-1. Purpose

The Headquarters, Medical Research and Development Command Institutional Review Board (HQ MRDC IRB) follows these policies and procedures to assure that the IRB functions in full compliance with the Federal, Department of Defense (DoD), Defense Health Agency (DHA), MRDC, 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 DHA and the Medical Research and Development Command (MRDC) are strongly committed to ensuring the protection of human subjects participating in research. The MRDC consists of institutions responsible for conducting, contracting, sponsoring, supporting, or managing human biomedical and socio-behavioral research. As such these institutions are entrusted with the responsibility to protect the human subjects in research.

b. The Director, DoD Office of Human Research Protections (DOHRP), Under Secretary of Defense for Research and Engineering (USD(R&E)), has delegated the authority and responsibilities set forth in DoD Instruction (DoDI) 3216.02, “Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and -Supported Research,” to the MRDC Senior Designated Official. The MRDC Senior Designated Official serves as the authority and assumes responsibility within the MRDC 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 DOHRP USD(R&E) has designated the MRDC Office of Human and Animal Research Oversight (OHARO) as a Component-level oversight office and delegated the MRDC OHARO Component-level authorities and human research protection official authority for the MRDC’s subordinate commands.

c. The MRDC Office of Human and Animal Research (OHARO) is the MRDC Headquarters (HQ) element charged with ensuring that MRDC conducted, contracted, sponsored, supported, or managed research involving human subjects, human anatomical substances or animals are conducted in accordance with (IAW) Federal, DoD, DHAMRDC, state, and international regulatory requirements. The Director, OHARO serves as the MRDC Human Protections Director (HPD).

d. All non-exempt human subjects research conducted or supported by the DoD must be reviewed and approved by a duly constituted Institutional Review Board (IRB); the HQ MRDC IRB provides this review and oversight for the organizations described in Chapter 2 of this

document. The IRB Office is a subordinate office within the OHARO and administers activities of the HQ MRDC IRB.

f. These policies and procedures describe how the MRDC OHARO and HQ MRDC IRB operationalize the current federal, DoD, DHA, MRDC, state, and international regulatory requirements for human subjects protection. These policies and procedures apply to the HQ MRDC IRB, the OHARO IRB Office and all organizations and personnel for whom the HQ MRDC IRB serves as IRB.

Any study approved by the IRB or determined exempt **on or after 21 January 2019** will follow the policies and procedures contained within this document. Any eligible study approved before 21 January 2019 may transition to the 2018 Common Rule. Once transitioned, a study will follow the policies and procedures explicated within this document, and may not return to the pre-2018 Common Rule requirements.

Any study approved or determined exempt prior to 21 January 2019 but that does not transition to the 2018 Common Rule requirements remains subject to the pre-2018 Common Rule requirements. Any study subject to other statutory or regulatory, e.g., Food and Drug Administration, or DOD/DHA requirements must follow those requirements in addition to these policies and procedures.

Chapter 2. Authority; Scope of Services; HQ MRDC IRB's and Relying Institutions' Roles and Responsibilities

2-1. Authority Granted to the HQ, MRDC IRB

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, D and E; and 21 CFR 50 and 56 set forth the requirements for review of non-exempt human subjects research by an IRB. The HQ MRDC IRB provides human subjects protection review, approval, and oversight of protocols IAW these regulations. The IRB has the authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this policy, including exempt research activities under §219.104 for which limited IRB review is a condition of exemption (under §219.104(d)(2)(iii), (d)(3)(i)(C), and (d)(7), and (8)).

b. Department of Defense Instruction (DoDI) 3216.02., "Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and -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. These protections adhere to the ethical principles of respect for persons, beneficence, and justice as described in the Belmont Report. The DoD Instruction implements 32 CFR 219 and 45 CFR 46, Subparts B, C and D, and their requirements for IRB review and approval of all non-exempt research involving human subjects.

2-2. Purpose

The primary mission of the HQ MRDC IRB is to protect the safety, rights, and welfare of subjects in research conducted under its purview. The IRB has a responsibility to ensure that research involving human subjects is conducted ethically and in compliance with applicable Federal, DoD and MRDC regulatory requirements.

The HQ MRDC IRB primarily supports institutions external to the HQ MRDC:

a. serving as the primary IRB for select MRDC subordinate commands and Army organizations (See Section 2-3); and

b. providing IRB review services on an *ad hoc*, per-protocol basis for institutions both within and outside the MRDC.

In either capacity, the HQ MRDC IRB may review single-site research protocols or may review on behalf of institutions engaged in multi-site or collaborative projects through the institution's role as a performance site, lead site, and/or coordinating center. Finally, the HQ MRDC IRB may serve as a central or single IRB (hereafter referred to as single IRB) in support of multi-institutional collaborative or multi-site research projects. As a single IRB, the HQ MRDC IRB serves as the sole IRB for all institutions engaged in the research protocol.

Sections 2-4 and 2-5 of this chapter outline the general division of responsibilities between the HQ MRDC IRB and relying institutions. Section 2-6 addresses additional considerations that apply when the HQ MRDC IRB functions as a single IRB for multi-site/collaborative research projects.

2-3. Scope of IRB Services

The HQ MRDC IRB provides IRB services for:

a. The MRDC Subordinate Institutes and Laboratories. The HQ MRDC IRB serves as the primary IRB for the US Army Aeromedical Research Laboratory (USAARL), the US Army Institute of Surgical Research (USAISR), the US Army Medical Research Institute of Infectious Diseases (USAMRIID), the US Army Research Institute of Environmental Medicine (USARIEM), the US Army Center for Environmental Health Research (USACEHR), the US Army Medical Research Institute of Chemical Defense (USAMRICD) and the Telemedicine and Advanced Technology Research Center (TATRC). Additionally, the HQ MRDC IRB may serve as a reviewing or single IRB on an *ad hoc*, per-protocol basis for protocols in which other MRDC Institutes and Laboratories participate.

b. Non-MRDC DoD institutions. The HQ MRDC IRB serves as the IRB for DoD institutions outside the MRDC as well as select civilian institutions involved in DoD collaborations. For these institutions, the division of responsibilities for human research protections is delineated in the DoD Institutional Agreements for IRB Review (IAIR) and/or in Memoranda of Agreement or Understanding with the respective institutions.

c. Force Health Protection (FHP) Investigational New Drug (IND) Protocols. The HQ MRDC IRB is designated in DoDI 6200.02 as the single IRB for review and approval of the DoD contingency IND protocols for FHP. Refer to Chapter 16 of this document for information regarding the HQ MRDC IRB's role in the review of contingency IND protocols for FHP.

d. Single IRB review for multi-site and collaborative research. DoDI 3216.02 requires use of a single institutional review board (IRB) in accordance with Section 219.114 of Title 32, CFR. As such, the HQ MRDC IRB may serve as a single IRB for research conducted at multiple institutions.

2-4. Shared Responsibilities of the Relying Institution and the HQ MRDC IRB

The HQ MRDC IRB has regulatory responsibility for the protection of the rights and welfare of research subjects from initial review to closure of the research protocol to IRB oversight. Each institution relying upon the IRB sets local standards, policies, and procedures related to the conduct of research at that institution. Together, the relying institution and the HQ MRDC IRB oversee the conduct of human subjects research. Shared responsibilities include:

a. Ensuring that the HQ MRDC and the relying institution have an IAIR (or other agreement) in place. The scope of the agreement may be limited to a specific protocol, a specified group of research protocols, or may apply to any research protocols upon prior written agreement from both institutions.

b. Identifying and defining roles and timeframes for reporting to the IRB, appropriate institutional officials, sponsors and federal and applicable state agencies; serious and continuing noncompliance with 32 CFR 219 or with requirements/determinations of the IRB; unanticipated problems involving risks to subjects or others; or suspension or termination of IRB approval.

c. Clearly communicating expectations, including regulatory requirements, sharing of information between the institution and the IRB, and a process for determining potential corrective/remedial actions in the event of noncompliance.

d. Developing a communication plan for sharing information about the site, the investigators, the sponsor, and study between the institution and the IRB, e.g., identifying the plan to evaluate investigator qualifications, communicating any substantive changes to the institution, its human research program, or the local research context in connection with the research to the HQ MRDC IRB and vice versa.

e. Identifying a process for responding to subject concerns and grievances, including coordination of communication to subjects.

f. As applicable, defining in writing any protocol-specific roles and responsibilities to achieve compliance with regulatory or other requirements that are not otherwise defined in the IAIR.

g. Ensuring execution of other agreements, such as a Memorandum of Understanding or Memorandum of Agreement as necessary to delineate unique requirements, e.g., payment for IRB services.

h. Defining roles and responsibilities for investigating allegations of noncompliance and determining potential corrective/remedial actions in the event of noncompliance;

i. Delineating roles and responsibilities and developing a process for post-approval compliance monitoring activities.

2-5 Responsibilities of Institutions Relying on the HQ MRDC IRB

Institutions relying on the HQ MRDC IRB will:

a. Maintain an approved Assurance. Note: individual investigators who are part of an institution without an Assurance may be covered by another institution's Assurance through an Individual Investigator Agreement (IIA) and must follow the relied-upon institution's requirements.

b. Communicate any relevant substantive changes to the institution, its human research program, or the local research context in connection with a study to the HQ MRDC IRB;

c. Comply with HQ MRDC IRB policies and procedures and with the terms of the IAIR.

d. Maintain and comply with their own institutional policies and procedures for the conduct of human subjects research (e.g., institution's HRPP plan);

e. Upon request, provide a copy of the institution's HRPP plan to the OHARO IRB Office to enable the OHARO IRB Office and HQ MRDC IRB to better understand the local mechanisms for human research protections;

f. On a per protocol basis, conduct a conflict of interest assessment and propose strategies to ensure that COIs are managed appropriately;

g. Maintain a program for education of its investigators and research staff and ongoing training in human subjects research and research protections;

h. As applicable, follow institutional and/or DoD component policies regarding update of their DoD Assurance and/or Federalwide Assurance, to reflect reliance on the HQ MRDC IRB and maintain documentation to support the update;

i. Perform institutional review of research protocols prior to submission to HQ MRDC IRB, e.g., review for feasibility, compliance with state/local and General Counsel requirements, scientific review standards (if applicable), and requirements by other relevant review committees;

j. Perform a complete regulatory compliance and quality review of all submitted research protocols and life cycle actions prior to submission to the HQ MRDC IRB;

k. Provide local context for the HQ MRDC IRB to consider during its review as needed/requested;

l. Provide written confirmation to the HQ MRDC IRB that all personnel who interact or intervene with human subjects, and/or their identified data and/or specimens in the research study have completed and are current in the appropriate human research protection training (documentation of training completion may be requested by the HQ, MRDC IRB on a case-by-case basis);

m. Confirm the credentials and qualifications of all investigators and key research personnel, and submit applicable documentation (e.g., current *Curriculum Vitae* or other documents) to the HQ MRDC IRB for review;

n. Ensure that investigators obtain final HQ MRDC IRB approval and any required local approvals, as applicable, before research may begin;

o. Ensure that investigators obtain any required local ancillary committee reviews, e.g., radiation safety, institutional biosafety;

p. Oversee and conduct post-approval monitoring of its research, to include for cause audits at the request of the HQ MRDC IRB of studies where the IRB has identified concerns, to ensure that the investigator/researcher conducts the research and recruitment of potential research subjects in accordance with the IRB-approved protocol, procedures, and documents. Provide results of post-approval monitoring activities to the HQ MRDC IRB that require IRB review or action;

q. As applicable, comply with requirements of the DoD Privacy Act and the DoD Health Information Privacy Regulation DoDI 6025.18 and DoD Manual 6025.18 which implements the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule;

r. Communicate with the HQ MRDC IRB as required by the HQ MRDC IRB Policies and Procedures (Chapter 18) and the institution's HRPP plan. At a minimum, relying institutions must report (1) unanticipated problems involving risks to subjects or others, (2) allegations of serious or continuing noncompliance, (3) institutional or investigator suspension or termination of research, and (4) any other events or circumstances requiring notification, (e.g., knowledge of pending compliance inspections by any DoD or non-DoD agencies);

s. Maintain research protocol records (e.g., Principal Investigator master files, subject study files) in accordance with applicable regulatory requirements, HQ MRDC IRB Policies and Procedures and with institutional policies.

2-6. Division of Responsibilities when the HQ MRDC IRB Serves as a Single IRB for Multi-site Research

a. Request for Single IRB Review. Program officials, HQ MRDC personnel and others must first submit a request to the Director, OHARO IRB Office for the HQ MRDC IRB to serve as a single IRB. The request may be made via formal memorandum, email, or during a telephone discussion. In order for the HQ MRDC IRB to consider serving as a single IRB for a given research effort:

(1) The lead research site must be a DoD institution;

(2) All institutions that wish to rely on the HQ MRDC IRB for the research project must possess an approved Federal Assurance (DoD institutions must possess a DoD Assurance);

(3) All engaged institutions must agree to fulfill the institutional responsibilities described in this policy and to enter into an IAIR or other agreement with the HQ MRDC.

b. In addition to adhering to the policies and procedures outlined throughout this document the HQ MRDC IRB serving as a single IRB will:

(1) Review submissions for new performance sites on a rolling basis;

(2) Evaluate whether the lead Principal Investigator's proposed management of information relevant to the protection of subjects across study sites is adequate;

(3) As feasible, align protocol IRB approval expiration dates across sites, where applicable, in order to synchronize continuing review intervals;

(4) Notify all relying institution(s) promptly of reportable events that have occurred at any individual relying institution. Per 32 CFR 219/21 CFR 56, reportable events include (a) unanticipated problems involving risks to subjects or others, (b) serious or continuing noncompliance, (c) suspension or termination of IRB approval, and (d) any other events or circumstances requiring notification (See Chapters 18, 20, 21 and 22). Based on the nature of the event, relying institutions may be notified prior to the HQ MRDC IRB's formal or official determination of whether a reportable event comprises one of these categories (e.g., an unexpected death on study), or may be notified following the HQ MRDC IRB's determination (e.g., allegation of noncompliance) and development of a corrective and preventive action plan;

c. The OHARO IRB Office supports the HQ MRDC IRB and the relying institution, and will:

(1) Verify, in consultation with the requesting Principal Investigator, institution, or others (e.g., Director, OHARO; CG, MRDC), whether specific research protocols are eligible for review by the HQ MRDC IRB as a single IRB;

(2) As needed, provide briefings or training for institutional personnel, such as the Institutional Official (IO), HPD, investigators, and others, on the respective roles and responsibilities when HQ MRDC IRB serves as the single IRB;

d. The Lead institution for multi-site research protocols will:

(1) Coordinate determination of eligibility of performance sites to be reviewed by the HQ MRDC IRB as a single IRB;

(2) Conduct or make provisions to obtain a scientific review of the core research protocol; or rely on a scientific review completed by a peer or national group, or other appropriate scientific review process and ensure that the scientific review determination is provided to the HQ MRDC IRB for consideration;

(3) Provide a communication plan for management of information relevant to the protection of subjects across all sites, such as reporting of unanticipated problems involving risks to subjects or others (UPIRTSOs), safety reports, interim results, and protocol modifications.

Chapter 3. Human Subjects Protection Education & Training Requirements

3-1. Background

For investigators, key research personnel, research monitors (when assigned), and HQ MRDC IRB members and OHARO IRB Office staff, human subjects protection training and continuing education are critical activities to assure the conduct of research in an ethical manner and protect subjects' safety, rights, autonomy, and welfare.

a. Investigators, key research personnel, and, when assigned, research monitors for protocols under the HQ MRDC IRB's purview, and HQ MRDC IRB members and OHARO IRB Office staff must complete initial human subjects research ethics training prior to beginning their relevant duties involving human subjects research, and must also complete continuing education at least every three (3) years, consistent with their roles and responsibilities in human subjects research.

b. In lieu of the training described below (in Section 3-2.b), the HQ MRDC IRB may accept documentation of human subjects protection training and continuing education for investigators, key research personnel, and research monitors from institutions with established requirements for this training.

c. Regulatory Basis for Training Requirements.

(1) Federal, DoD, and Army regulations and guidance documents require:

(a) That all DoD personnel involved in the conduct, review, or approval of research involving human subjects, including the non-affiliated and prisoner representative members on the DoD IRB, receive initial and continuing education and training;

(b) Initial and continuing education commensurate with the duties and responsibilities of the DoD personnel; and

(c) Documentation of training and education.

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

(3) MRDC subordinate commands must also comply with MRDC Command Policy Memorandum, "Requirements for Initial and Ongoing Education and Training in the Protection of Human Subjects in Research."

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 and delegation of authority log who have direct contact with subjects or their identifiable records, data, and/or specimens), and, when assigned, research monitors involved in human research projects where the HQ MRDC IRB serves as the reviewing IRB;

(2) HQ MRDC IRB members and OHARO IRB Office leadership; and

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

b. Specific Training Requirements.

(1) Investigators, key research personnel, and research monitors (when assigned) from DoD institutions. The HPD or designee from a DoD research institution must provide written confirmation (e.g. a signed protocol submission checklist) attesting that all study personnel have completed and remain current in required human subjects protection training appropriate to their role in the research.

(2) Investigators, key research personnel, and research monitors (when assigned) from non-DoD institutions. These personnel must comply as follows:

(a) Investigators and key research personnel conducting, and, when assigned, research monitors overseeing Biomedical research: Completion of 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 HQ MRDC IRB education requirements. Continuing education in human subjects protection must be completed every three (3) years by either completion of the entire CITI course for biomedical focused research or equivalent continuing education training.

(b) Investigators and key research personnel conducting, and, when assigned, research monitors overseeing Social-Behavioral research: Completion of modules of the CITI, web-based, self-contained course for socio-behavioral focused research at http://www.citiprogram.org/, meets the initial HQ MRDC IRB education requirements. Continuing education in human subjects protection must be completed every three (3) years by either completion of the entire CITI course for socio-behavioral focused research or equivalent continuing education training.

(c) Biomedical and Social-Behavioral investigators, key research personnel, and, when assigned, research monitors must also fulfill the human subjects protections training requirements found in the August 16, 2012 ASD(R&E) memorandum, “Minimum Education Requirements for DoD Personnel Involved in Human Research Protection,” by completing training in DoD-unique content not found within the standard CITI human subjects protection coursework.

(3) HQ MRDC IRB members, Chair, Vice Chair, and OHARO IRB Office Leadership. These personnel must comply as follows:

(a) HQ MRDC IRB members, Chair, Vice Chair, and OHARO IRB Office leadership are responsible for the completion of modules of the CITI, web-based course 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 completion of the assigned CITI modules or equivalent continuing education training.

(b) In addition to completion of CITI training, HQ MRDC IRB members must complete initial training in the IRB’s responsibility for implementation of the provisions of the HIPAA Privacy Rule and must also fulfill the human subjects protections training requirements found in

the August 16, 2012 ASD(R&E) memorandum, “Minimum Education Requirements for DoD Personnel Involved in Human Research Protection,” by completing training in DoD-unique content not found within the standard CITI human subjects protection coursework.

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

(d) The HQ MRDC IRB Chair and/or Vice Chair and/or IRB Office leadership 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 MRDC IRB, and the primary review process;

(3) Encourage members to participate actively in HQ MRDC IRB meetings;

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

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

(1) Regulation-based presentations when unique cases or actions come before the Board.

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

(3) Brief presentations of highlights and trends from meetings, conferences, or site visits by the HQ MRDC IRB members or the OHARO staff.

(4) OHARO IRB Office HSPSs (whose responsibilities include the conduct of pre-reviews and life cycle management of protocols for which the HQ MRDC IRB serves as the reviewing IRB). In addition to CITI and DoD-unique training requirements as noted above for IRB members, HSPSs are encouraged to attend one HQ MRDC IRB meeting per month during the calendar year. Attendance at conferences related to human subjects protection and the conduct of clinical research every two to three 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 MRDC IRB as the reviewing IRB are responsible for acting in accordance with specific laws, regulations, policies, procedures, and guidance applicable to the HQ MRDC 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 MRDC IRB Office Leadership. The Director and Deputy Director of the IRB Office 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/research monitors: Human subjects research ethics education and training documentation will be maintained by the HPD or designee in the institution's regulatory file. The HPD or designee will confirm that all study team members' required HRP/GCP training is current and appropriate, based on the institution's HRPP, and will submit written confirmation to the HQ MRDC IRB Office with the protocol submission.

(2) For HQ MRDC IRB members, Chair, Vice Chair, and IRB Office leadership: All human subjects research ethics training will be entered in a tracking database by IRB Office staff upon completion. The HQ MRDC IRB members will be notified by email of the need to complete refresher training in advance of expiration of training.

(3) For OHARO IRB Office HSPSs: All human subjects research ethics training will be entered upon completion and tracked by IRB Office staff in a tracking database. OHARO IRB Office HSPSs are required to complete refresher training in advance of expiration of training.

b. HSPS. HSPSs conducting pre-reviews and life cycle management of protocols are responsible for verifying that the HPD or designee has provided written confirmation that all study team members' required HRP/GCP training is current and appropriate, based on the institution's HRPP.

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

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

This chapter describes the primary and alternate membership, appointment and meeting quorum requirements.

4-1. Membership Composition

The HQ MRDC 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, to ensure that members possess knowledge, experience, scientific, or scholarly expertise in the types of protocols most frequently reviewed by the Board. In addition, to serve as the DoD IRB responsible for reviewing FDA-regulated expanded access protocols in which the President of the United States (POTUS) could waive the requirement for advance informed consent for military Service Members, the HQ MRDC IRB must also fulfill the unique board composition requirements detailed by the FDA in 21 CFR 50.23.

a. Qualifications. The HQ MRDC IRB members will be sufficiently qualified and have the necessary experience, expertise, and community sensitivity to adequately review research activities presented to the HQ MRDC IRB.

b. Membership Diversity. The HQ MRDC IRB is constituted IAW the requirements of 32 CFR 219/21 CFR 56.107. The IRB is comprised of a minimum of seven primary members, of varying backgrounds with regard to branch of military 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 will be diverse in terms of cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to determine the acceptability of proposed research in terms of institutional commitments (including policies and resources) and regulations, applicable law, and standards of professional conduct and practice. The IRB shall therefore include persons knowledgeable in these areas. When the IRB reviews research that involves a category of subjects that is vulnerable to coercion or undue influence, such as children, prisoners, individuals with impaired decision-making capacity, or economically or educationally disadvantaged persons, the IRB will include one or more individuals who are knowledgeable about and experienced in working with these categories of subjects. The IRB includes at least one member whose primary concerns are in scientific areas, and at least one member whose primary concerns are in nonscientific areas.

c. Non-Affiliated Members. The regulations at 32 CFR 219.107 require at least one member who is not affiliated with the institution among the IRB membership (i.e., not otherwise affiliated with the institution and who is not part of the immediate family of a person who is affiliated with the institution). However, IAW 10 USC 1107, 21 CFR 50.23, and DoDI 6200.02, there are additional membership requirements with which the HQ MRDC IRB must comply as the IRB responsible for review and approval of the DoD contingency IND protocols for FHP. Under 10 USC 1107 the POTUS may waive the prior consent requirement for the administration of an IND to a member of the Armed Forces in connection with the member's participation in a particular military operation; 21 CFR 50.23 specifies that the IRB's membership must include at least three members who are not affiliated with the federal government for the review of protocols for which the Secretary of Defense requests such waiver from the POTUS. Consequently, the HQ MRDC IRB will include at least three individuals among its membership who are unaffiliated with the federal government, except for the purpose of membership on the HQ MRDC IRB.

d. Members from Organizations Served by the HQ MRDC IRB. The HQ MRDC IRB aims to include members representing the MRDC Institutes and Laboratories for which it serves as the primary IRB, as well as members of the United States Navy and United States Air Force to represent the interests of all uniformed services in the research conducted within the DoD. During periods when the HQ MRDC IRB supports review of research conducted in a theater of operations, individuals who have deployment experience will be sought for membership.

e. Primary Members. The HQ MRDC IRB will include the following among its primary members:

(1) Two or more certified healthcare providers (e.g., board-certified physicians, certified nurse practitioners).

(2) A military or civilian attorney within the MRDC Office of the Staff Judge Advocate (OSJA).

(3) A chaplain and/or bioethicist.

(4) A non-scientist member able to represent the general perspective of research subjects.

(5) One officer and one enlisted active duty or retired service member.

(6) One member who is not affiliated with the federal government (except for purposes of membership on the HQ MRDC IRB)

(7) A scientist member who brings expertise in research design and methodology.

f. Vulnerable Subjects. When the HQ MRDC IRB reviews research that involves a vulnerable category of subjects, such as children, individuals with impaired decision-making ability , individuals with acute or severe mental illness, or those who are economically or educationally disadvantaged, one or more individuals who specifically represent concerns of these subject populations will attend the meeting or provide written comments. Should the HQ MRDC IRB review research involving prisoners as subjects, it will comply with the additional requirements of 45 CFR 46.304 with regard to membership composition and meeting quorum.

g. Consultants. The HQ MRDC 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.

h. Requirement for Federal Employment. HQ MRDC IRB members designated Expedited Review Approval Authority 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. IRB Members designated Expedited Review Approval Authority who are not federal employees must be engaged as IPAs or intermittent consultants IAW 5 USC 3109 for this purpose.

i. Alternate Members. The background of an alternate member should be similar to the member he or she is replacing (or he or she should be able to represent similar interests).

Although an alternate may be qualified to replace more than one primary member, only one primary member may be represented by the alternate at any convened meeting. If both the alternate and the primary member attend a meeting, only one of these two individuals may vote. When an alternate member substitutes for a primary IRB member, the alternate member will receive and review the same material that the primary member received or would have received. Meeting minutes must document when an alternate member replaces a voting member. At least one alternate will be designated for the non-affiliated member.

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

a. The HQ MRDC IRB Chair and/or Director, OHARO recommend potential members to the CG, MRDC, who serves as the HQ MRDC's Institutional Official (IO) or Deputy Commander, MRDC, who serves as the Deputy Institutional Official (DIO). The CG or Deputy Commander, MRDC, appoints HQ MRDC IRB members for four year terms. There is no limit to the number of terms an IRB member may serve.

(1) The IRB Chair. This function will ideally be filled by a physician or Doctor of Philosophy (PhD) with human subjects protection and clinical research experience. The Chair presides over convened meetings and serves as a voting member. The IRB Chair directs the IRB meetings in accordance with institutional and federal requirements. The Chair works closely with IRB members and IRB Office staff, as well as researchers, to ensure the rights and welfare of research subjects are protected. The Chair also serves as the principal signatory official for IRB correspondence; however, may designate other IRB members or IRB Office administrative staff to sign select IRB documents, such as Research Monitor appointment memos. The Chair is responsible for conducting expedited reviews, reviewing reportable events, and reviewing materials submitted for the emergency use of investigational drugs, devices or biologics. The Chair may delegate a responsibility or responsibilities to any IRB member as he or she deems appropriate.

(2) IRB Vice Chairs. This function will be filled by individuals with human subjects protection and human subjects research experience. A Vice Chair serves as a voting member and will preside over convened meetings in the absence of the Chair.

b. In accordance with 32 CFR 219/21 CFR 56.110.(b)(2), one or more experienced HQ MRDC IRB members can be designated to perform expedited reviews and approvals. The HQ MRDC IRB Chair, Vice Chair or OHARO IRB Director will assess whether a member possesses the requisite level of experience to perform expedited reviews and approvals, taking into account demonstrated knowledge and ability to apply ethical principles and human subjects protection regulations, his/her longevity on the HQ MRDC IRB, past IRB experience, the quality and timeliness of primary/secondary reviewer assignments, and will make designations in writing.

c. An Acting Chair can be drawn from among the experienced HQ MRDC 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. Additionally, an Acting Chair may be designated by the CG or Deputy Commander, MRDC 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 only at a convened

meeting that meets quorum requirements. Of the members required to be present for quorum to be met, one must be an individual whose primary concerns are in nonscientific areas.

(1) To count towards the quorum, attendance must be in person, by video/online 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 219/21 CFR 56.108).

(3) Should the quorum be lost 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 MRDC Office of the Staff Judge Advocate (SJA) must render an opinion identifying any legal concerns before a formal HQ MRDC 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), three non-affiliated and non-federal 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 POTUS.

Chapter 5. Conflict of Interest of IRB Members/Staff, Researchers and the Organization

This chapter describes the requirement for management of financial and other conflicts of interest for HQ MRDC IRB members and OHARO IRB Office staff members; investigators and research team members; and organizations/institutions.

5-1. Background

a. Conflict of interest (COI). 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 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 financial interest with respect to a protocol when he/she and or his/her immediate family receives any of the following:

(a) Compensation, the value of which 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, the value of which cannot be readily determined through preference to public prices (e.g., ownership interest or stock options);

(d) Any equity interest in the sponsor or product;

(e) Payments of other sorts made directly by the sponsor as a research or educational grant, equipment, consultation, or honoraria, or other payment.

Financial interest does ***not*** include:

(a) Salary or other remuneration from the MRDC or employee's institution;

(b) Income from seminars, lectures, or other teaching engagements sponsored by public agencies (i.e., Federal, state, or local government) 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.

(2) Other Conflicts of Interest. There are some COIs that are non-financial in nature. Other examples of COI that could apply to HQ MRDC IRB members/staff and/or investigators/research staff include:

(a) Employer/employee or other hierarchical relationships.

(b) Potential for personal reward.

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

a. Rationale for Prohibition of COI. It is essential that members of the HQ MRDC IRB, subject matter expert consultants, and OHARO IRB Office support staff (e.g., Director and Deputy Director, IRB Office, HSPSs) remain free from any COI between their personal interests and/or their official capacity outside the IRB, and their HQ MRDC IRB responsibilities in regard to the protocols they review. It is the policy of the HQ MRDC IRB that IRB members, subject matter expert consultants, and OHARO 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. IRB members, subject matter expert consultants, and OHARO IRB Office support staff must declare all potential or actual COI before review of any research under HQ MRDC 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 MRDC 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. The HQ MRDC IRB is not in a direct reporting line to those within the MRDC who fund or have an interest in the research that the IRB reviews. The OHARO has a direct reporting line through the Deputy Commander, MRDC, thus shielding the IRB from undue influence within the HQ MRDC.

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 MRDC IRB member may not deliberate or vote on a protocol if the member feels that s/he has been subject to undue command influence to approve the protocol.

c. Procedure. At the beginning of each HQ MRDC IRB meeting, the Chair will ask if any IRB members have COIs regarding any of the protocols before the Board. Members must disclose all potential or actual conflicts and recuse themselves from deliberating or voting on the protocol(s) with which they have a COI, and leave the meeting room during the Board's deliberations and vote. Additionally, Board members assigned as primary or secondary reviewers, or as expedited reviewers, will alert the OHARO IRB Office staff if they have a COI or potential COI with the protocol. The OHARO IRB Office will assign a new primary, secondary, or expedited reviewer.

d. Additional Requirements for the Chair, Director and Deputy Director, OHARO IRB Office, and Other Designated Federal Personnel. Additional requirements for annual disclosure of assets, liabilities, and outside positions apply to federal employees in covered positions who must complete US Office of Government Ethics, Confidential Financial Disclosure Report (OGE 450) and complete annual Ethics Training. The purpose of these reports and training is to assist federal employees and their agencies in avoiding conflicts between duties and private financial interests or affiliations.

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.

b. Investigator/Research Staff Disclosure Requirement. All key study personnel, i.e., those individuals who will have direct contact with subjects or their identifiable data or specimens, must disclose to their institution's regulatory office or HQ MRDC IRB any financial interest with a research sponsor, and any other financial interest that may reasonably appear to affect or be affected by the research.

(1) Each investigator/key research staff member will submit a COI Disclosure Form. The disclosure must:

(a) be in writing;

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

(c) list all financial interests of the individual and/or his/her family member(s) with a research sponsor, and all financial or other 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 conflicts of interest that may reasonably appear to affect or be affected by the research.”

(f) be dated and signed by the individual;

(g) be submitted along with the protocol to the institution’s regulatory office or the IRB, as applicable.

(2) The research staff member must update his/her COI disclosure if s/he acquires new financial interests with a research sponsor, or new financial or other 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). Additionally, the Principal Investigator must submit verification that there are no new COIs to disclose at the time of the research protocol’s continuing review.

b. Eliminating, Managing, or Reducing COIs. The institution’s regulatory office or HQ MRDC IRB, as applicable, will review the COI disclosure forms as part of the initial or life-cycle action review of the research protocol. If the institution’s regulatory office or HQ MRDC IRB determines that any of the disclosed interests are COIs, the IRB will evaluate whether the proposed mitigation plan is acceptable or make additional recommendations regarding 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/research staff member cannot eliminate a COI, s/he 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 the consent document;

(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 MRDC IRB will not approve research until it is satisfied that COIs have been or will be eliminated or appropriately/sufficiently managed or reduced.

c. Disclosure to Subjects in the Consent document. If the HQ MRDC IRB believes that a COI cannot be eliminated, and that the COI could be considered material to a potential subject's decision-making process (e.g., when a subject assesses 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 COI Disclosure Statements. The institution's regulatory office will maintain records of COI disclosures and actions taken with respect to each COI as part of the research master file and retain documentation in accordance with the requirements at 32 CFR 219/21 CFR 56.115.

e. Confidentiality of Financial Disclosure Statements. To the extent permitted by law, the institution's regulatory office or, when applicable, HQ MRDC 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 institution's regulatory office or, when applicable, HQ MRDC 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 MRDC 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 if 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.

5-4. Organizational Conflict of Interest

a. Organizational COIs may arise when the financial investments or holdings of an organization (including licenses, royalties, intellectual property rights, patents, certain gifts) or the personal financial interests or holdings of a key leader might affect or reasonably appear to affect organizational processes for the design, conduct, reporting, review, or oversight of human subjects research.

b. The OHARO IRB Office, Institution's regulatory office or HQ MRDC IRB may identify potential organizational COIs that exist within the HQ MRDC or at any of the institutions that rely upon the HQ MRDC IRB. For research under its purview, the HQ MRDC IRB is sensitive to potential organizational COIs, and works to eliminate and/or ensure the organization with the COI appropriately manages any COI prior to approving the project. As necessary, the IRB will consult with other entities, e.g., Director, OHARO; IO of the relying institution, Staff Judge Advocate Office, etc.

Chapter 6. Determinations of "Not Research" or Research Not Involving Human Subjects

Projects determined to be not research or research but not involving human subjects are not subject to the provisions of 32 CFR 219.

6-1. Authority for making "Not Research" or "Research Not Involving Human Subjects" Determinations

The assessment of an activity as research, or research not involving human subjects, is made by OHARO IRB Office federal staff members designated to do so i.e., the Director and Deputy Director, OHARO IRB Office or by the HQ MRDC IRB Chair, Vice Chair, or a designated IRB member. Individuals delegated to make determinations are designated as Exempt Determination Officials (EDO).

6-2. Determining an Activity is "Not Research"

a. The initial step in applying the appropriate framework for review of a given project is assessing whether the activity is "research" as defined in 32 CFR 219.102(l).

(1) Activities are not research as defined in 32 CFR 219.102(l) if they do not involve a systematic investigation (e.g., involving a predetermined method(s) 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 subjects or human subject 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), Quality or Performance Improvement (QI, PI) activities designed to improve the quality or performance of a department or program where it is not the intention to share or generalize resultant data beyond the immediate community conducting the activity.

(d) Case reports or case series e.g., a report describing a patient's or group of patients' course of care (where there has not been a systematic manipulation of patient interventions to produce generalizable results).

(e) Scholarly and journalistic activities (e.g. oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collection.

(f) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors,

patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(g) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(h) Authorized operational activities carried out solely in support of the DOD mission to provide military forces needed to deter war and to protect the security of the U.S. These activities are subject to approval by the Head of the Component or Secretary of Defense, including heads of subordinate agencies that have been delegated authority to study, evaluate, improve or otherwise examine DoD performance, quality and capability, and which otherwise do not meet the definition of research in this Instruction.

(2) There are also activities conducted or supported by the DoD that do NOT comprise research involving human subjects as defined in the "Definitions" section of the DoDI 3216.02 e.g., program evaluation and surveys, user surveys, outcome reviews, and other methods, designed solely to assess the performance of DoD programs where the results of the evaluation are only for the use of Government officials responsible for the operation or oversight of the program being evaluated.

6-3. Determining an Activity as Research Not Involving Human Subjects

a. If an activity meets the regulatory definition of research, it is further assessed to determine whether the research involves "human subjects" as defined in 32 CFR 219.102(e).

b. An activity deemed research not involving human subjects as defined in 32 CFR 219.102(e), may not involve:

(1) obtaining biospecimens or information about the individual through intervention or interaction with individual subjects, and using, studying, or analyzing the information or biospecimens; or

(2) obtaining, using, studying, analyzing or generating identifiable private information or identifiable biospecimens.

c. Examples of activities that would be considered research not involving human subjects include, but are not limited to:

(1) 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.

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

(3) Research involving testing of new equipment in which no data *about* the individual operator(s) are collected.

6-4. 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)). Note: Army conducted or supported research with cadaveric materials is subject to the requirements of the Army Policy for Use of Human Cadavers for Research, Development, Test and Evaluation, Education or Training.

6-5. Documenting Determinations

The EDO documents the rationale for the determinations by way of a regulatory-based checklist. The HPD or EDO maintains the determination in the institution’s regulatory files.

6-6. “Not Research” and Research Not Involving Human Subjects Determination Notifications

The IRB Office notifies the investigator and his/her institution, in writing, of a determination that the project is not subject to the regulatory requirements in 32 CFR 219.

6-7. Changes in Projects Previously Determined to be “Not research” or “Research Not Involving Human Subjects”

An investigator must submit any change to the project that could affect the determination status for a review by the OHARO IRB Office / EDO prior to implementation.

Chapter 7. Human Subjects Research Review

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

7-1. Scientific Peer Review of Research

DoDI 3216.02 requires DoD IRBs to document their consideration of scientific merit; within the consideration of scientific merit, feasibility of study completion should be considered. Scientific peer review ensures that research is scientifically sound in its design and methods, and the proposed research is worthy of performance.

The HQ MRDC IRB requires that documentation of prior criteria-based scientific review of a proposal / protocol accompany its submission for IRB review; the HQ MRDC IRB considers the scientific review and feasibility of study completion during the IRB review process.

Documentation should demonstrate that the scientific review assessed the following criteria, as appropriate, given the scholarly field and objectives of the study: (a) the rationale for the study is clearly stated and is scientifically sound; (b) the hypothesis or study aims are clearly stated; (c) the objectives or outcomes are clearly stated; (d) there are adequate preliminary data provided in the protocol to justify the proposed research; (e) an adequate literature review was done to support the study; (f) the question or hypothesis tested is of sufficient scientific merit to justify the study; (g) the design of the study is appropriate; (h) the validity and reliability of proposed measures have been established or there are methods proposed for establishing validity and reliability; (i) the proposed subject population is appropriate; (j) statistical considerations, including sample size and statistical analysis techniques, are clearly described and adequate; (k) proposed tests or interventions are required to answer the study objectives; (l) the Principal Investigator and all other investigators are qualified to conduct the proposed study.

7-2. Reviews by Other Organizations/Committees

a. At times, research may be subject to regulatory review and approval of other organizations or committees such as the Food and Drug Administration (FDA), Recombinant DNA Advisory Committee, etc. Research managers, Sponsors and Principal Investigators are responsible for ensuring that required reviews take place. As appropriate, the HQ MRDC IRB may request documentation that required committee reviews and approvals are in place prior to initiating IRB review 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 IRB approval. The HQ MRDC IRB requests applicable letters of support to be submitted with a protocol submission.

c. Institutional Reviews. Institutions must complete internal reviews, such as Biosafety Committee, Radioactive Drug Research Committee, Radiation Safety Committee, prior to submission, e.g., review for feasibility and institutional/departmental support and compliance with state and local requirements. Institutions must review for compliance with local General Counsel requirements and local scientific review standards (if applicable). Finally, local institutions must review letters of support/impact statements from departments and compliance with other local requirements identified by relevant internal review committees.

d. 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 Service Members conducted in two or more DoD Components (Services) must be approved by the Washington Headquarters Service, IAW DoDI 1100.13 (Surveys of DoD Personnel).

e. Other DoD 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 components' facilities or with their personnel.

7-3. Pre-review and Determination of Review Pathway by the OHARO IRB Office

Protocols submitted to the OHARO IRB Office for review by the HQ MRDC IRB are forwarded to the IRB Office leadership (the Director, IRB Office and Deputy Director, IRB Office are referred to as leadership for the HQ MRDC IRB) 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. The IRB Office leadership reviews all HSPS pre-review recommendations along with the submission package prior to requesting additional information or revisions from the Principal Investigator. The Chair, Vice Chair, HQ MRDC IRB member or the IRB Office leadership makes the final assessment regarding whether the activity is non-exempt human subjects research, and whether the project qualifies for expedited review or requires full Board review.

The OHARO IRB Office also evaluates projects and protocols to assess institutional engagement, generally following the concepts described in the DHHS OHRP's October 16, 2008 "Guidance on Engagement of Institutions in Human Subjects Research". Evaluation of institutional engagement ensures that non-exempt human subjects research receives appropriate IRB review. The institution's regulatory office or OHARO IRB Office staff assess whether, for the purposes of the research project, employees of the institution obtain: (1) data about the subjects of the research through intervention or interaction with them; (2) identifiable private information about the subjects of the research; or (3) the informed consent of human subjects for the research. During pre-review, the institution's regulatory office or IRB Office staff conduct a detailed assessment of all institutions listed within the protocol as supporting the study to determine their role in the research (e.g., awardee, performance site, lead site, performance of a service), and of the study activities undertaken at each institution (e.g., direct interaction with subjects or their identifiable data, analysis of identifiable data or specimens). The institution's regulatory office or OHARO IRB Office staff then confirm that all engaged institutions possess an appropriate Federal Assurance and have agreed to rely on the HQ MRDC IRB for review. For institutions whose role and activities do not engage them in non-exempt human subjects research, the institution's regulatory office or OHARO IRB Office ensures that the institution has visibility of their personnel's collaboration on the activity and will confirm the institution has performed a determination on behalf of their personnel.

Additionally, the institution's regulatory office or OHARO IRB Office assesses all project and protocol submissions to determine whether they require a Component-level Administrative Review (see Chapter 26 for additional information), Headquarters-level Administrative Review or a Human Research Protection Official (HRPO) review and approval as required by DoDI 3216.02. The Director, IRB Office and Deputy Director, IRB Office are designated Human Research Protection Officials authorized to perform HRPO reviews and issue approvals.

The Director or Deputy Director, IRB Office and/or the assigned HSPS identify the requirement for a Human Research Protection Official review in addition to IRB review during the IRB Office pre-review process. OHARO IRB Office staff receives training in Human Research Protection Official reviews from the MRDC OHARO, Office of Human Research Oversight (OHARO OHRO), and work closely with the OHARO OHRO to coordinate Human Research Protection Official reviews. The MRDC IRB protocol template, submission checklist, and pre-review checklists solicit specific information regarding collaborating institutions and DoD support or assistance through funding, facilities, equipment, personnel (investigators or other personnel performing tasks identified in the research protocol), access to or information about DoD personnel for recruitment, or identifiable data or specimens from living individuals.

When the HQ MRDC IRB serves as the single reviewing IRB pursuant to Part 219 of Title 32, CFR, the IRB review and approval will constitute the HRPO review and approval; an additional HRPO review is not required. For protocols reviewed by the HQ MRDC IRB that also require Human Research Protection Official review the approval of initial or life-cycle action by the HQ MRDC IRB will include a statement noting that in accordance with DoDI 3216.02, section 3.6, approval from a DoD Human Research Protection Official is not required as the research, including oversight of any non-DoD partners, is approved by a DoD IRB.

7-4. Exempt Human Subjects Research

a. Certain categories of research involving human subjects are exempt from the regulatory requirements of 32 CFR 219. Exempt research activities should adhere to the fundamental ethical principles outlined in the Belmont Report. The eight categories of research that are exempt from the federal regulations are found in 32 CFR 219.104. Only exempt category #6 applies to research that is also FDA-regulated. Department or agency heads may make the final determination of whether a given research protocol is exempt (32 CFR 219.104(c)). Although 32 CFR 219 does not address the risk level of exempt human subjects research, it must present little or no risk to subjects.

(1) Exempt Category #1: [32 CFR 219.104(d)(1)] Research, conducted in established or commonly accepted educational settings, that specifically involves normal educational practices that are not likely to adversely impact students' opportunity to learn required educational content or the assessment of educators who provide instruction. This includes most research on regular and special education instructional strategies, and research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

(2) Exempt Category #2: [32 CFR 219.104(d)(2)] Research that only includes interactions involving educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior (including visual or auditory recording) if at least one of the following criteria is met:

(a) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects [32 CFR 219.104(d)(2)(i)];

(b) Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation [32 CFR 219.104(d)(2)(ii)]; or

(c) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §219.111(a)(7) [[32 CFR 219.104(d)(2)(iii)].

(3) Exempt Category #3: [32 CFR 219.104(d)(3)]

(a) Research involving benign behavioral interventions in conjunction with the collection of information from an adult subject through verbal or written responses (including data entry) or audiovisual recording if the subject prospectively agrees to the intervention and information collection and at least one of the following criteria is met [32 CFR 219.104(d)(3)(i)]:

1 The information obtained is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained, directly or through identifiers linked to the subjects;

2 Any disclosure of the human subjects' responses outside the research would not reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation; or

3 The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects, and an IRB conducts a limited IRB review to make the determination required by §219.111(a)(7).

(b) For the purpose of this provision, benign behavioral interventions are brief in duration, harmless, painless, not physically invasive, not likely to have a significant adverse lasting impact on the subjects, and the investigator has no reason to think the subjects will find the interventions offensive or embarrassing. Provided all such criteria are met, examples of such benign behavioral interventions would include having the subjects play an online game, having them solve puzzles under various noise conditions, comparing test performance of test takers in quiet or noisy surroundings, or having them decide how to allocate a nominal amount of received cash between themselves and someone else [32 CFR 219.104(d)(3)(ii)].

(c) If the research involves deceiving the subjects regarding the nature or purposes of the research, this exemption is not applicable unless the subject authorizes the deception through a prospective agreement to participate in research in circumstances in which the subject is informed that he or she will be unaware of or misled regarding the nature or purposes of the research [32 CFR 219.104(d)(3)(iii)]..

(4) Exempt Category #4: [32 CFR 219.104(d)(4)] Secondary research for which consent is not required: Secondary research uses of identifiable private information or identifiable biospecimens, if at least one of the following criteria is met:

(a) The identifiable private information or identifiable biospecimens are publicly available [32 CFR 219.104(d)(4)(i)];

(b) Information, which may include information about biospecimens, is recorded by the investigator in such a manner that the identity of the human subjects cannot readily be ascertained directly or through identifiers linked to the subjects, the investigator does not contact the subjects, and the investigator will not re-identify subjects [32 CFR 219.104(d)(4)(ii);

(c) The research involves only information collection and analysis involving the investigator's use of identifiable health information when that use is regulated under 45 CFR parts 160 and 164, subparts A and E, for the purposes of “health care operations” or “research” as those terms are defined at 45 CFR 164.501 or for “public health activities and purposes” as described under 45 CFR 164.512(b) [32 CFR 219.104(d)(4)(iii)]; or

[NOTE: Category #4(iii) only applies to a valid Health Insurance Portability and Accountability Act (HIPAA) authorization, waiver of HIPAA authorization issued by the IRB in its capacity as the Privacy Board, or an approved and executed HIPAA-compliant Data Use Agreement for use or disclosure of a limited data set comprised of protected health information]

(d) The research is conducted by, or on behalf of, a Federal department or agency using government-generated or government-collected information obtained for nonresearch activities, if the research generates identifiable private information that is or will be maintained on information technology that is subject to and in compliance with section 208(b) of the E-Government Act of 2002, 44 U.S.C. 3501 note, if all of the identifiable private information collected, used, or generated as part of the activity will be maintained in systems of records subject to the Privacy Act of 1974, 5 U.S.C. 552a, and, if applicable, the information used in the research was collected subject to the Paperwork Reduction Act of 1995, 44 U.S.C. 3501 *et seq .* [32 CFR 219.104(d)(4)(iv)].

[NOTE: Category #4(iv) only applies when adequate documentation that the applicable requirements have been satisfied, including at a minimum compliance with 44 USC 3501 et seq. (Federal Information Privacy); a published System of Records Notice (SORN); and if applicable, approval in accordance with the Paperwork Reduction Act]

(5) Exempt Category #5: [32 CFR 219.104(d)(5)] Research and demonstration projects that are conducted or supported by a Federal department or agency, or otherwise subject to the approval of department or agency heads (or the approval of the heads of bureaus or other subordinate agencies that have been delegated authority to conduct the research and demonstration projects), and that are designed to study, evaluate, improve, or otherwise examine public benefit or service programs, including procedures for obtaining benefits or services under those programs, possible changes in or alternatives to those programs or procedures, or possible changes in methods or levels of payment for benefits or services under those programs. Such projects include, but are not limited to, internal studies by Federal employees, and studies under contracts or consulting arrangements, cooperative agreements, or grants. Exempt projects also include waivers of otherwise mandatory requirements using authorities such as sections 1115 and 1115A of the Social Security Act, as amended.

Each Federal department or agency conducting or supporting the research and demonstration projects must establish, on a publicly accessible Federal Web site or in such other manner as the department or agency head may determine, a list of the research and demonstration projects that the Federal department or agency conducts or supports under this provision. The research or demonstration project must be published on this list prior to commencing the research involving human subjects.

(6) Exempt Category #6: [32 CFR 219.104(d)(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 US Department of Agriculture.

NOTE: *Exempt categories #7 and #8 always require limited IRB review and are only available when broad consent will be (or as applicable, has been) obtained. However, until DOD and/or Army guidance is issued, these exemptions shall not be used for DOD-conducted research, separately or in collaboration with a non-DOD institution, in which research the DOD institution stores, maintains or uses DOD identifiable private information or identifiable biospecimens. Once DOD and/or Army guidance has been provided, Categories #7 and #8 may be used as described above*.

(7) Exempt Category #7: [32 CFR 219.104(d)(7)] Storage or maintenance for secondary research for which broad consent is required: Storage or maintenance of identifiable private information or identifiable biospecimens for potential secondary research use if an IRB conducts a limited IRB review and makes the determinations required by §219.111(a)(8).

(8) Exempt Category #8: [32 CFR 219.104(d)(8)] Secondary research for which broad consent is required: Research involving the use of identifiable private information or identifiable biospecimens for secondary research use, if the following criteria are met:

(a) Broad consent for the storage, maintenance, and secondary research use of the identifiable private information or identifiable biospecimens was obtained in accordance with §219.116(a)(1) through (4), (a)(6), and (d) [32 CFR 219.104(d)(8)(i)];

(b) Documentation of informed consent or waiver of documentation of consent was obtained in accordance with §219.117 [32 CFR 219.104(d)(8)(ii)];

(c) An IRB conducts a limited IRB review and makes the determination required by §219.111(a)(7) and makes the determination that the research to be conducted is within the scope of the broad consent referenced in (8)(i) of this section [32 CFR 219.104(d)(8)(iii)]; and

(d) The investigator does not include returning individual research results to subjects as part of the study plan. This provision does not prevent an investigator from abiding by any legal requirements to return individual research results [32 CFR 219.104(d)(8)(iv)].

b. Limitations on Exemptions. For research involving children, category #2(i) and #2(ii) do NOT apply except for research involving educational tests or observations of public behavior when the investigator does not participate in the activities being observed. Exempt category #2(iii) is NOT applicable to research involving children. Exempt category #(3) does NOT apply to research involving children. For research involving prisoners, the exemptions do not apply EXCEPT for research aimed at involving a broader subject population that only incidentally includes prisoners.

c. Documenting Exempt Determinations. A designated OHARO IRB Office federal staff member reviews and documents by way of a regulatory-based checklist that the research meets one or more of the exemption categories under 32 CFR 219.104(d).

d. Exempt Determination Notifications. The IRB Office notifies the investigator and his/her institution, 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.

e. Previously Determined Exempt Research - An investigator must submit any change to an exempt research activity that could affect the determination status for a review by the OHARO IRB Office prior to implementation.

7-5. Limited IRB Review

a. Limited IRB review is a type of review required in 32 CFR 219 for four of the exemption categories (see 7-4a above).

b. For exemption categories 2 and 3, the purpose of a limited IRB review is to ensure privacy/confidentiality protections are in place to reduce the chance of inappropriate disclosure of sensitive, identifiable data. The requirement for limited IRB review is triggered when:

(1) The information obtained is recorded by the investigator in such a manner that the identity of the human subjects can readily be ascertained, directly or through identifiers linked to the subjects; AND

(2) Any disclosure of the human subjects' responses outside the research would reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, educational advancement, or reputation.

c. For exemption categories 7 and 8 where broad consent will be, or has been obtained, limited IRB review is always required. The purpose of a limited IRB review for these types of exempt research is to ascertain whether broad consent was obtained for the use of stored identifiable data or biospecimens, and documented according to an approved protocol (if appropriate).

d. For exempt studies involving access to protected health information (PHI), e.g., from medical records, the required Privacy Board review may be integrated with limited IRB review by the same assigned IRB reviewer.

e. Reviewing and Documenting Limited IRB Reviews - A limited IRB review will be conducted using expedited review procedures using a regulatory-based checklist, by the HQ MRDC IRB Chair, Vice Chair, or by a designated expedited reviewer. As with all other research subject to IRB review requirements, when conducting limited IRB review, the reviewer exercises 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 MRDC IRB in accordance with the procedure in 32 CFR 219.108(b).

f. Limited IRB Review Notifications - The IRB Office notifies the institution requesting the limited IRB review and/or the investigator , 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 appropriate, and the outcome of the IRB's limited review.

g. Proposed modifications to the aspects of research subject to limited IRB review must be submitted to and approved by the IRB prior to implementation, except when necessary to

eliminate apparent immediate hazards to the subject(s). In this case the change must be promptly report to the IRB (i.e. within 5 business days of implementation).

h. Continuing Review for Exempt Research Requiring Limited IRB Review – Continuing review is not required for exempt human research.

7-6. "Expedited" Review

a. An expedited review procedure consists of the review of non-exempt human subjects research by the HQ MRDC IRB Chair, Vice Chair, or by an experienced reviewer designated from among the IRB members IAW the requirements in 32 CFR 219/21 CFR 56.110. 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 MRDC IRB in accordance with the procedure in 32 CFR 219.108(b).

b. The IRB may use the expedited review procedure to review the following:

(1) Research appearing on the most current Federal Register list of categories of research eligible for expedited IRB review. Research within this list of categories is presumed to be *no more than minimal risk.* If the IRB determines and documents the research to involve *more than* minimal risk, the research will be referred to the convened IRB for review.

(2) Minor changes in previously approved research during the period of one year or less for which approval is authorized (32 CFR 219/21 CFR 56.110(b)(2)).

(a) A minor change is one in which, in the judgment of the IRB expedited reviewer, does not add procedures involving increased risk or discomfort; does not significantly alter the risk/benefit assessment the IRB relied upon to approve the protocol; does not involve the addition of procedures, interactions, or interventions that add significant medical, social, or psychological risks; does not involve addition of a vulnerable population in research not otherwise eligible for expedited review; does not significantly alter the scientific question or validity of the study; does not substantially alter the IRB's original conditions of approval; and would not be expected to impact a subject's decision to participate or remain in the research.

(b) Common examples of minor changes in approved research include administrative amendments; editorial changes that clarify but do not alter the existing meaning of a document; additional versions of approved consent documents, recruitment posters, or advertisements; and changes in study staff.

(c) Addition of new performance sites/investigators for protocols not eligible for initial review by expedited procedure may be considered for expedited review as minor changes. The IRB reviewer must determine that addition of the site/investigators would not increase risk to subjects, and must consider such criteria as:

1. The site's qualifications, e.g., ability to provide oversight and monitoring of the study, availability of infrastructure and ancillary support services, adequacy of the facility including the availability of emergency or specialized care.

2. The investigators' qualifications, e.g., education, experience in the area of research, existence of financial or other COIs, compliance history.

c. Expedited review is as substantive as convened IRB review, i.e., the same approval criteria apply. The IRB member conducting the expedited review receives and reviews the same protocol materials that are required for convened board reviews.

d. The requirements for informed consent (or its waiver or alteration), considerations for the applicability of 10 USC 980, and additional protections for vulnerable populations apply to protocols eligible for expedited review..

e. The IRB Office notifies the investigator and his/her institution, in writing, of the IRB's approval, including the applicable expedited review category(ies) under which the research activity was reviewed and approved.

7-7. Nine Categories of Research Approvable by Expedited Review

In conducting an expedited protocol review, the HQ MRDC IRB Chair, Vice Chair, or designated IRB reviewer will consider criteria for approval identified in 32 CFR 219/21 CFR 56.111 and other applicable laws, regulations, or policies. Initial (and 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 children[2], 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."

7-8. Convened IRB Meetings and Reviews

All protocols not eligible for expedited review and approval will be reviewed by the convened HQ MRDC IRB. Meetings are generally held twice per month. The IRB will meet if there are protocols or other agenda items for review, and may schedule meetings on an *ad hoc* basis when necessary.

OHARO IRB Office staff contact HQ MRDC IRB members approximately two weeks prior to scheduled meetings by email or telephone to determine their availability for the meeting. The IRB Office leadership evaluates the types and volume of protocol actions on the meeting agenda to ensure members with appropriate expertise will attend and that there will be sufficient time for the IRB to discuss and evaluate each agenda item. The IRB will defer to another meeting or obtain subject matter expert consultation if there is not at least one member available for the meeting with appropriate scientific or scholarly expertise or knowledge to conduct an in-depth review of protocol actions on a meeting agenda.

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

(1) At least three to five business days prior to an IRB meeting, read-ahead packets of materials for review at that meeting are delivered electronically to each attending IRB member. All members of the HQ MRDC IRB are provided the same documentation in their read-ahead packets. All IRB members expected to actively participate in the review and discussion of the protocol.

(2) The read-ahead packets contain the protocols and supporting materials or other actions for review, an agenda with primary/secondary reviewer member assignments, minutes from previous IRB meetings (when available), educational materials, and other administrative items as necessary.

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

(a) A document/checklist summarizing a pre-review of the protocol, to include identified regulatory issues and observations for consideration by the IRB;

(b) Expert consultant report and recommendations (as necessary);

(c) Consent document(s) and/or assent forms (when applicable);

(d) Copy of the full protocol;

(e) Documentation of scientific review;

(f) *Curriculum vitae* (CVs) of the Principal Investigator, Associate Investigators and ombudsperson(s);

(g) Study instruments;

(h) Advertisements and other recruitment materials;

(i) Investigator's Brochure, Device Manual, product and/or device information as applicable;

(j) Additional correspondence, as needed;

(k) Other regulatory documents as appropriate.

(l) All modified documents (for amendments to previously approved research).

b. Use of a Primary Reviewer System.

(1) In order to promote a thorough review of protocols, the HQ MRDC IRB uses a primary reviewer system in which studies are assigned to one or more attending 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 and secondary reviewers.

(3) Primary and secondary reviewers are provided a review checklist to aid in their assessment and presentation of the protocol. Review summaries completed by an IRB reviewer(s) before the meeting is/are circulated to all attending Board members.

c. Responsibilities of the IRB Members and Meeting Conduct.

(1) All IRB members are encouraged to contact the IRB Office staff, Principal Investigator, or other study team member to discuss questions prior to the scheduled IRB meeting.

(2) Conflict of Interest.

(a) As described in Chapter 5 of this document, no HQ MRDC 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 MRDC 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 interest is required to fully disclose that interest. The Board may discuss and decide if a member's reported interest poses a conflict; if a COI exists, the member will 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 or call prior to deliberations and vote.

(3) Review and Acceptance of Minutes from Previous HQ MRDC IRB Meetings. Minutes from previous HQ MRDC IRB meetings are presented to members attending convened IRB meetings. 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.

(4) Review and Acceptance of the List of Protocols and Protocol Actions Reviewed Via Expedited Procedure. As required under 32 CFR 219/21 CFR 56.110(c), all attending HQ MRDC IRB members will be advised of protocol actions approved, since the last convened meeting, using expedited review procedures, to include actions reviewed by limited IRB review, by provision of a list and description of such approvals. This information will be included in the read-ahead materials for IRB meetings and/or delivered to members via electronic mail. Members are offered the opportunity to ask questions or obtain additional information about any action reviewed using the expedited review procedure.

(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 reviewer(s) to provide a summary of the protocol and any issues identified during review. Research team members may be requested to present a brief summary of the protocol, as appropriate. If a subject matter expert was consulted, s/he will be asked to provide written comments and attend the meeting if possible. If attending, the Chair and members will ask the consultant about his/her observations and any recommendations for the protocol. After general discussion of the protocol, the Principal Investigator (and research team members) may be invited to answer questions posed by the IRB.

(b) The Principal Investigator or 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 and all IRB members during the review process.

(c) No research team members will be present during the IRB discussion and voting period. Any HQ MRDC IRB members with a COI will also leave the room or disconnect from the teleconference. The IRB will consider whether the criteria for approval of human subjects research as described in Chapter 8 of this document are met, and if applicable, whether the requirements of 10 USC 980 are addressed (See 8-7). After a final discussion and deliberation of remaining issues, to include a determination of study risk level, any stipulations and the period of approval will be agreed upon (see Section 6-9.d(7)), a motion will be made and seconded (see Section 6-9.d(8)), 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).

(6) The HQ MRDC IRB will consider the criteria for approval identified in 32 CFR 219/21 CFR 56.111 and other applicable laws, regulations, or policies. The HQ MRDC IRB can make the following decisions regarding a review action.

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

1. For initial reviews, the motion and vote will also include the period (not longer than one year) for which the initial approval is valid.

2. The IRB Office will provide IRB approval to the Principal Investigator, the institution, and other appropriate interested parties once all stipulations set by the IRB have been met by the Principal Investigator.

(b) Conditional Approval. Consistent with the DHHS OHRP's 2010 "Guidance on IRB Approval of Research with Conditions", the IRB may approve research with conditions if given the scope and nature of the conditions, the IRB is able to make all of the determination required for approval under 32 CFR 111 and any applicable subparts (B, C, or D) of 45CFR 46.

1. The IRB may require the following as conditions of approval of research:

a. Confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted (e.g., confirmation that the research excludes children);

b. Submission of additional documentation (e.g., certificate of human subjects protection training);

c. Precise language changes to protocol or informed consent documents; or

d. Substantive changes to protocol or informed consent documents along with clearly stated parameters that the changes must satisfy.

2. At the time of conditional approval, the IRB may choose to designate a single IRB member or subcommittee of two or more members to review and verify responses to the IRB's stipulations to determine that the conditions for approval set by the IRB have been satisfied. An IRB Office staff member will forward the IRB's required stipulations to secure approval, including considerations, in writing to the Principal Investigator within three business days following the IRB meeting.

3. The response to the IRB's stipulations will be reviewed by the IRB Office staff prior to dissemination to the IRB designated reviewer(s). The protocol/review action becomes IRB-approved upon verification by the IRB member that the conditions of approval have been met and/or the information has been provided by the IRB designated reviewer. For initial reviews, the protocol's expiration date is set based on the date of verification by the IRB designated reviewer that stipulations are fully addressed.

(c) Deferral. The IRB action is taken when the IRB cannot fully evaluate the research under review and make the necessary determinations required for approval due to substantive concerns or lack of clarity about the conduct of the protocol and/or safety of the subjects, the IRB's inability to determine that the criteria for IRB approval are met, and/or inability to specify changes to the research protocol that if made would allow the IRB to approve the protocol or life cycle action.

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

2. The IRB Office staff will forward the IRB's specific stipulations and recommendations in writing to the Principal Investigator.

3. The Principal Investigator must address all of the IRB's stipulations and recommendations before the IRB Office will submit the PI's response to the IRB for review.

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

(d) Disapproval. An IRB action taken when the determinations required for approval of research in 32 CFR 219.111 cannot be made, even with substantive clarifications or modifications to the protocol and/or informed consent process/document.

1. The IRB Office will communicate the IRB's disapproval of a research study in writing to the Principal Investigator, the institution, 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.

2. Any protocol disapproved by the IRB may be resubmitted, but only with a complete summary of responses to all of the IRB concerns.

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

(a) 32 CFR 219.108(3)(ii) and 21 CFR 56.108(a)(2) require 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 no more than one year from the date of approval, the HQ MRDC 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 exists.

3. Protocols involving novel procedures with unknown risks and hazards.

4. Protocols involving a high frequency of amendments.

5. Protocols with a number of unexpected adverse events or other unanticipated problems.

6. Situations involving investigators, institutions, or other contextual factors for which the HQ MRDC IRB has reason for increased vigilance.

7. Protocols from investigators who are known to have not complied with regulatory requirements in the past.

(b) As an alternative to requiring conduct of continuing review in less than 12 months, the HQ MRDC IRB may require a review after a specific number of subjects have been enrolled and/or 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 Research 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 MRDC IRB recommends an approval period shorter than 12 months, the IRB's rationale for the shorter term of approval will be documented in the IRB minutes along with any requirements the investigator must fulfill by the end of this period.

(8) Meeting Minutes. The IRB Chair, Vice Chair, or Acting Chair who presided over the meeting will review the draft minutes, make any necessary edits, and then sign the minutes. As needed/identified by the Chair or Director, OHARO, the Director or Deputy Director, IRB Office, will prepare an Executive Summary for the CG, MRDC describing any unique or controversial issues from the meeting for his/her visibility.

7-9. Approval Authority of the Research Institution

Research subject to the HQ MRDC IRB's review may not be approved for implementation by any DoD official unless it has first been approved by the IRB. An official at any level may not overturn the HQ MRDC IRB's disapproval, deferral, or conditional approval, nor does any official have the authority to reduce or waive safeguards, restrictions, or stipulations that IRB recommends in a conditional approval.

7-10. Appeal Process

a. An investigator may appeal an IRB decision if he or she believes that the process was not fair, the decision was arbitrary or capricious, or did not have an appropriate ethical or regulatory basis. Not agreeing with an IRB decision is not appropriate grounds for appealing an IRB decision.

b. If the IRB makes a decision that the investigator believes to be unduly restrictive on the proposed research, the investigator should first discuss the matter with the IRB Chair. Investigators may appeal the decisions of the HQ MRDC IRB in writing, documenting the reasons for the appeal within 30 days of being notified in writing of the IRB's decision. Investigators shall provide the written appeal along with any supporting documents through their Institutional Official to the OHARO IRB Office. The HQ MRDC 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 convened IRB will review the appeal, and the Principal Investigator will be invited to attend the meeting to present the protocol and address issues surrounding the appeal. The Full Board will vote to accept or reject the appeal.

c. Written notification of the HQ MRDC IRB's decision of the appeal will be sent to the Principal Investigator and his/her Institutional Official following the meeting. An IRB decision will be issued within sixty days from receipt of the appeal from the investigator. An IRB decision may only be submitted for appeal once to the IRB.

d. If, following this appeal process the matter under appeal remains unresolved, the IRB Director or Deputy Director will coordinate consultation/mediation through the Director, OHARO. No person or entity within the HQ MRDC can overrule disapprovals by the IRB.

Chapter 8. Knowledge of Local Research Context

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

8-1. Background

a. The regulations at 32 CFR 219/21 CFR 56.107(a) requires that IRBs be sufficiently qualified through the diversity of the members, including race, gender, and cultural backgrounds and sensitivity to such issues as community attitudes, to promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects. The IRB shall be able to ascertain the acceptability of proposed research in terms of institutional commitments (including policies and resources) 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 219.111/21 CFR 56.111(a)(3),(a)(4),(a)(7),(b).

8-2. Consideration of Local Research Context by the HQ MRDC IRB

a. The HQ MRDC IRB's geographic distance from the majority of Institutions for which it serves as IRB necessitates the IRB members' and OHARO IRB Office staff awareness and evaluation of important site-related issues during its review of protocols. Considerations include:

(1) The anticipated scope of the research activities;

(2) The types of subject populations likely to be involved;

(3) The size, complexity, and experience of the institution and its researchers 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.

(14) Availability of medical or psychosocial resources that subjects may need as a consequence of the research.

(15) Plans for transitioning investigator roles based on the movement between military assignments.

b. The HQ MRDC 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 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 MRDC IRB, the OHARO 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 Director (HPD);

(d) Review of relevant written materials such as institutional HRPP plans, 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 subjects.

c. The HQ MRDC IRB will apply knowledge of the local research context to ensure:

(1) Equitable subject selection;

(2) Protection of subjects' privacy and maintenance of data confidentiality;

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

(4) Existence of appropriate safeguards to protect the rights and welfare of vulnerable subjects and special populations;

(5) Respect for local cultural, religious, and community norms;

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

d. Research reviewed by the HQ MRDC IRB is subject to local laws, i.e., those of the state or country in which the research is conducted. Examples of local laws that may be relevant to research reviewed by the IRB include:

(1) Defining age of majority;

(2) Reporting of abuse;

(3) Reporting of infectious diseases;

(4) Reporting of sepsis;

(5) Defining who can serve as legally authorized representative (LAR).

Chapter 9. Criteria for Approval of Human Subjects Research

This chapter describes the criteria that must be met for the HQ MRDC IRB to approve non-exempt human subjects research. These criteria apply to human research reviewed by expedited or convened-Board review procedures and to initial review, continuing review and review of modifications to previously approved research (when the modification affects a criterion for approval).

9-1. Approval Criteria for Exempt Research Reviewed by Limited IRB Review

a. When conducting a limited IRB review, the HQ MRDC IRB will not determine whether the proposed research meets the requirements set forth below in section 9-2 a(1) through a(6).

b. For exempt categories #2(iii) and #3(i), the IRB will approve the research when it determines that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

c. For exempt category #7, the following criteria must be satisfied:

(1) Broad consent for storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens is obtained in accordance with the requirements of 32 CFR 219.116(a)(1) - (4), (a)(6), and (d);

(2) Broad consent is appropriately documented or waiver of documentation is appropriate, in accordance with 32 CFR 219.117; and

(3) If there is a change made for research purposes in the way the identifiable private information or identifiable biospecimens are stored or maintained, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data.

(a) The IRB will consider the following to evaluate whether research satisfies exempt category 7:

(i) The extent to which identifiable private information is or has been de-identified and the risk that such de-identified information can be re-identified;

(ii) The use of the information;

(iii) The extent to which the information will be shared or transferred to a third party or otherwise disclosed or released;

(iv) The likely retention period or life of the information;

(v) The security controls that are in place to protect the confidentiality and integrity of the information; and

(vi) The potential risk of harm to individuals should the information be lost, stolen, compromised, or otherwise used in a way contrary to the contours of the research under the exemption.

d. For exempt category #8, the IRB may approve the research when it determines that the following criteria are satisfied:

(1) There are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data; and

(2) The research to be conducted is within the scope of the broad consent obtained from subjects.

9-2. Approval Criteria (the "7 in 111") for Non-Exempt Research

a. The HQ MRDC IRB determines that all of the following requirements set forth in 32 CFR 219/21 CFR 56.111 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.

The HQ MRDC IRB will consider all potential risks, to include physical, psychological, social, economic, and legal risks when evaluating research risks.

Appointment of a Research Monitor. The IRB may appoint an independent research monitor for research protocols where it determines that additional protections are needed [e.g. research involving administration of test articles (e.g. FDA-regulated drugs, devices, biologics) that have not previously been tested in human subjects (i.e. "first in human") and for which no safety data in humans exist]. If required by the IRB, the name of the research monitor must be included in the protocol and his/her CV must be provided to the HQ MRDC IRB members, who will ensure appointment of an appropriate individual.

(a) This individual will possess the appropriate level of expertise consistent with the protocol to which s/he is assigned. More than one research monitor may be appointed if different skills or experiences are needed depending on the type of protocol or risks that might occur during the study.

(b) The HQ MRDC IRB will review and approve a written summary of the monitor's duties, taking into consideration:

(1) Specific risks and/or concerns about the research.

(2) The adequacy of the protocol's description of the monitor's oversight functions and plan for prompt reporting of observations and findings to the IRB and institution.

(3) The independence of the monitor with respect to the research team.

(c) In the event a research monitor is no longer able to fulfill their duties, the study PI must inform the IRB Office and their institution's HPD, and is responsible for ensuring a replacement research monitor is assigned to the research protocol.

(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, individuals with impaired decision-making ability, or economically or educationally disadvantaged persons.

(4) Informed consent will be sought from each prospective subject or the subject's LAR, in accordance with and to the extent required by 32 CFR 219.116/21 CFR 50.

(5) Informed consent will be appropriately documented, in accordance with and to the extent required by 32 CFR 219.117 / 21 CFR 56.109(c)(1).

(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, children, prisoners, individuals with impaired decision-making ability, or economically or educationally disadvantaged persons, the IRB will consider additional safeguards to protect the rights and welfare of these subjects.

9-3. Requirements for Informed Consent

a. The HQ MRDC 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, when appropriate, before involving a subject in research in accordance with and to the extent required by 32 CFR 219.116 and 21 CFR 50.116 for FDA-regulated research.

Additionally, the IRB considers the 10 USC 980 requirements for advance informed consent for humans involved in research as experimental subjects. LAR consent may only be allowed if each subject has the potential to benefit from the participation in the study (to include subjects participating in a placebo or standard of care arm).

The IRB reviews the informed consent document to determine whether it is consistent with the protocol plan and its stated risks and benefits, Investigator's brochure, and Sponsor's or Investigator's protocol, and contains the necessary elements of informed consent as required by the federal regulations. The IRB may request 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. The IRB will ensure that information communicated in the consent document does not include exculpatory language that waives or appears to waive any of the subject's legal rights or to release the investigator, sponsor, organization, or its agents from liability for negligence. The IRB may also require that information, in addition to that required in federal regulations, be given to

research subjects when in its judgment the information would meaningfully add to the protection of the rights and welfare of subjects.

b. Informed consent is an exchange of information between the research team and the study subjects throughout the course of a research study. Informed consent process must (please note the IRB will not approve a request to alter or omit items (1) through (6) below):

(1) Allow the prospective subject or the subject's LAR sufficient opportunity to discuss and consider whether or not to participate;

(2) Be solicited under conditions that minimize the possibility of undue influence or coercion (e.g., the IRB will review proposed payments to subjects to determine that the amount, method and timing of payment will not have undue influence on subjects);

(3) Use language understandable to the subject or the legally authorized representative subject;

(4) Provide information that a reasonable person would want to have in order to make an informed decision about whether to participate, and an opportunity to discuss that information;

(5) Present, as a whole, information in sufficient detail relating to the research, and must be organized and presented in a way that does not merely provide lists of isolated facts, but rather facilitates the prospective subject's or LAR's understanding of the reasons why one might or might not want to participate;

(6) Not waive or appear to waive subjects' or legally authorized representatives' rights through any exculpatory language; and

(7) Include each of the basic elements of informed consent describing the research and the nature of research participation as required by federal regulations. The basic elements of informed consent include:

(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 subject 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 subject;

(h) A description of how confidentiality of records identifying the subject will be maintained, and the identification of the entities who may have access to and review research records, to include the institution(s), the IRB, the DoD, and the FDA (for FDA-regulated studies);

(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 subject is otherwise entitled, and the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

(l) One of the following statements about any research that involves the collection of identifiable private information or identifiable biospecimens:

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

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

(8) Additional Elements of Informed Consent. 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 subject (or the embryo or fetus, if the subject 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 subject's or the legally authorized representative's consent;

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

(d) The consequences of a subject'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 subject's willingness to continue participation will be provided to the subject;

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

(g) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(h) A statement regarding whether clinically relevant research results, including individual research results, will be disclosed to subjects, and if so, under what conditions;

(i) A statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(j) For research involving biospecimens, a statement whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen).

9-4 Elements of Broad Consent.

a. As noted previously, until DOD and/or Army guidance is issued, exempt categories 7 and 8, and therefore broad consent, *shall not be used in DOD-conducted research*, separately or in collaboration with a non-DOD institution, in which research the DOD institution stores, maintains or uses DOD identifiable private information or identifiable biospecimens.

However, upon issuance of such DOD and/or Army guidance, broad consent must be obtained for: the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or nonresearch purposes) is permitted under the 2018 Requirements. *Note that broad consent is not currently recognized in FDA regulation or guidance.*

b. When obtaining broad consent, the general requirements for informed consent described above apply except as noted. The following elements of broad consent shall be provided to each subject or the subject's LAR:

(1) A description of any reasonably foreseeable risks or discomforts to the subject;

(2) A description of any benefits to the subject or to others which may reasonably be expected from the research;

(3) A statement describing the extent, if any, to which confidentiality of records identifying the subject must be maintained;

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

(5) For research involving biospecimens, a statement that the subject's biospecimens (even if identifiers are removed) may be used for commercial profit and whether the subject will or will not share in this commercial profit;

(6) For research involving biospecimens, whether the research will (if known) or might include whole genome sequencing (i.e., sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen);

(7) A general description of the types of research that may be conducted with the identifiable private information or identifiable biospecimens. This description must include sufficient information such that a reasonable person would expect that the broad consent would permit the types of research conducted;

(8) A description of the identifiable private information or identifiable biospecimens that might be used in research, whether sharing of identifiable private information or identifiable biospecimens might occur, and the types of institutions or researchers that might conduct research with the identifiable private information or identifiable biospecimens;

(9) A description of the period of time that the identifiable private information or identifiable biospecimens may be stored and maintained (which period of time could be indefinite), and a description of the period of time that the identifiable private information or identifiable biospecimens may be used for research purposes (which period of time could be indefinite);

(10) Unless the subject or legally authorized representative will be provided details about specific research studies, a statement that they will not be informed of the details of any specific research studies that might be conducted using the subject's identifiable private information or identifiable biospecimens, including the purposes of the research, and that they might have chosen not to consent to some of those specific research studies;

(11) Unless it is known that clinically relevant research results, including individual research results, will be disclosed to the subject in all circumstances, a statement that such results may not be disclosed to the subject; and

(12) An explanation of whom to contact for answers to questions about the subject's rights and about storage and use of the subject's identifiable private information or identifiable biospecimens, and whom to contact in the event of a research-related harm.

c. In their submissions to the IRB, investigators must include information regarding the circumstances under which broad consent will be obtained, the proposal for tracking of responses, and the proposed consent form(s) (or oral script if a waiver of documentation of consent is sought) and any other consent materials (e.g., information sheet, audiovisual materials, etc.).

d. When investigators propose research involving the use of identifiable private information and/or identifiable biospecimens research for which broad consent was obtained, the investigators must include documentation of the IRB approval for the storage or maintenance of the information or specimens and a copy of the consent form and any other consent materials.

9-5. Waiver or Alteration of Informed Consent

a. 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 subject; and

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects; and

(3) The research could not practicably be carried out without the waiver or alteration; and

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

(5) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

b. The FDA permits, as stated in the FDA Guidance dated July 2017 and titled "IRB Waiver or Alteration of Informed Consent for Clinical Investigations Involving No More than Minimal Risk to Human Subjects", an IRB to approve a consent procedure that does not include, or that alters, some or all of the elements of informed consent set forth in 21 CFR 50.25, or waive the requirements to obtain informed consent when the IRB finds and documents that:

(1) The clinical investigation involves no more than minimal risk (as defined in 21 CFR 50.3(k) or 56.102(i)) to the subjects;

(2) The waiver or alteration will not adversely affect the rights and welfare of the subjects;

(3) The clinical investigation could not practicably be carried out without the waiver or alteration; and

(4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

FDA does not intend to object to a sponsor initiating, or an investigator conducting, a minimal risk clinical investigation for which an IRB waives or alters the informed consent requirements as described above.

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

d. For research involving public benefit and service programs, the IRB may approve a request from an investigator to waive the requirement for informed consent, or to omit or alter one or more basic or additional element of consent if the below criteria are satisfied:

(1) The research or demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

(a) Public benefit or service programs;

(b) Procedures for obtaining benefits or services under those programs;

(c) Possible changes in or alternatives to those programs or procedures; or

(d) Possible changes in methods or levels of payment for benefits or services under those programs; and

(2) The research could not practicably be carried out without the waiver or alteration.

9-6. Documentation of Informed Consent for Human Subjects Research

a. Unless specifically waived or altered by the HQ MRDC IRB, there are two options for documentation of informed consent.

(1) Written consent document signed and dated by the subject or LAR (including in an electronic format), when appropriate.

(a) In most circumstances, the HQ MRDC IRB will require that informed consent is documented by the use of a written consent document approved by the IRB and signed by the subject or the subject's LAR, when appropriate.

(b) This consent document must embody, in language understandable to the subject or the subject's LAR, when appropriate, all the required elements necessary for legally effective informed consent. The required elements of informed consent as described in this document, in addition to any applicable additional elements that are required by the federal regulations must be included.

(c) The consent document may be read to the subject or the subject's legally authorized representative. However, the Investigator should allow the subject or the LAR 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, the HQ MRDC IRB may consider approval for use of oral presentation of informed consent information (e.g., with illiterate subjects). The subject 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 subject or the subject's LAR; and a written summary of the information that is presented orally. The IRB must approve the written summary of what is said to the subject or the subject's LAR. The short form must contain information that is most likely to assist a prospective subject or LAR in understanding the reasons why one might or might not want to participate in the research. As in a consent form, this information must be presented in an understandable format and be organized and presented in a way that facilitates comprehension.

(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 subject or the LAR 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 MRDC IRB may approve a process that allows delivery of the informed consent document by mail, email, or facsimile to the potential subject or the potential subject's LAR and to conduct the consent interview by telephone when the subject or the LAR 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.

9-7. Waiver of Documentation of Informed Consent

The HQ MRDC IRB may waive the requirement for the Investigator to obtain a signed consent document for some or all subjects. A waiver of documentation means that the requirement to obtain a *signed* consent document is waived, however, a consent process must still take place. A waiver of documentation may be 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 must be communicated to the subject verbally (if contact occurred by telephone) or in writing (as part of a survey cover sheet or information sheet provided to the subject), but a signed consent document is not required. In order to waive the requirement for documentation of informed consent the IRB must find:

a. That the only record linking the subject and the research would be the consent document and the principal risk would be potential harm resulting from a breach of confidentiality. In this instance, the investigator will ask each subject (or LAR) whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern (32 CFR 219.117(c)(1)(i)); or

b. That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context (32 CFR 219.117(c)(1)(ii)/21 CFR 56.109(c)(2)); or

c. That, if the subjects or LARs are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained ((32 CFR 219.117(c)(1)(iii)).

c. In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research.

d. For FDA-regulated research, only the option described in paragraph b above applies.

9-8. Informed Consent and Non-English Speaking Subjects

a. It is preferable that the written informed consent documents for non-English speaking subjects embody, in a language understandable to the subject, 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.

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 subject must be given copies of the short

form informed consent document and the summary. When this procedure is used with subjects 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 subject;

(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 subject should be present.

c. When consent will be obtained in a language other than English, documentation that the foreign language version of the consent document is an accurate translation of the English version of the consent document must be provided to the HQ MRDC IRB. A qualified translator provide documentation certifying the accuracy of consent document's translation along with the English and foreign language version of the consent documents. 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, and phone number of the translator. The HQ MRDC IRB may also request a back-translation certified as accurate by the translator.

9-9. DoD-, Army-, and HQ MRDC-Specific Review Requirements

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

a. 10 USC 980. Limitation on the Use of Humans as Experimental Subjects. 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 –

(1) the informed consent of the subject is obtained in advance; or

(2) in the case of research intended to be beneficial to the subject, the informed consent 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 LAR 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 decisionally impaired individuals or minors problematic. Investigators must be able to articulate how their research intends to benefit individual subjects if the subjects 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 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 DoDI 3216.02, the Secretary of Defense delegated this waiver authority to the DOHRP or its delegate. In accordance with DoDI 3216.02, the advance informed consent requirement pursuant to 10 USC 980 may be waived by the DOHRP or its delegate, if all the following conditions are met:

(1) The research is to advance the development of a medical product necessary to the DoD.

(2) The research may directly benefit the individual experimental subject.

(3) The research is conducted in compliance with all other applicable laws and regulations.

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 MRDC 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 US Department of Health and Human Services (HHS) regulations.

b. DoD Personnel as Subjects. The HQ MRDC IRB will give special consideration to recruitment and enrollment processes for DoD personnel participating in research as required by DoDI 3216.02 section 3.8.f. The HQ MRDC IRB will consider:

(1) The adequacy of informed consent provisions to inform DoD-affiliated personnel about risks to their fitness for duty (e.g. health, availability to perform job, data breach) and that they should seek command or Component guidance before participating.

(2) The adequacy of protocol compliance with the requirement that if the HSR involves DoD-affiliated personnel, the key investigator must receive command or Component approval to execute the research.

(3) The adequacy of protocol provisions to prohibit superiors (e.g., military and civilian supervisors, unit officers, and noncommissioned officers (NCOs)) from influencing decisions of subordinates regarding participation.

(4) Protocol provisions to prevent military and civilian supervisors, officers, and others in the chain of command from being present at any human subject recruitment sessions or during the consent process for DoD-affiliated personnel.. Excluded supervisors or those in the chain of command may participate in separate HSR recruitment sessions, if applicable.

(5) The adequacy of the recruitment process and the necessity of including Service members, Reserve Component or National Guard members in federal duty status, students at a Service Academy, or trainee under 18 years of age, as a human subject. Service members and all Reserve Component and National Guard members in a federal duty status are considered for purposes of the DoDI 3216.02, to be adults.

(6) Whether the following requirements have been satisfied in order to approve research involving DoD-affiliated personnel as human subjects:

(a) The consent documentation includes, if applicable, potential risks for the revocation of clearance, credentials, or other privileged access or duty.

(b) Appointment of an ombudsperson for research involving recruitment of DoD-affiliated personnel determined greater than minimal risk, as defined by Part 219 of Title 32, CFR, and when recruitment occurs in a group setting. The ombudsperson:

(1) Must not have a conflict of interest with the research or be a part of the research team.

(2) Must be present during the HSR recruitment, monitoring that the recruitment and informed consent explain that participation is voluntary and that the information provided about the research is consistent with the IRB-approved script and materials, including digitally provided materials.

(3) Should be available to address DoD-affiliated personnel's concerns about participation.

When appropriate, the IRB may appoint an ombudsperson for minimal risk research involving DoD-affiliated personnel recruited in a group setting, taking into account the human subject population, the consent process, and the recruitment strategy.

c. Payment for Study Participation for DoD-affiliated Personnel. Under Section 30 of Title 24, U.S.C., payment to DoD-affiliated personnel (Service members, Reserve Service members, National Guard members, and DoD civilians) for participation in research while on duty is limited to blood donation and may not exceed $50 per blood draw. DoD-affiliated personnel research subjects may not receive any other payment for participation in a research study. This $50 limitation applies only when DoD-affiliated 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 subjects (in a reasonable amount as approved by the IRB). Limitations exist regarding the source of payments exist for federal personnel:

Duty Status	Limitations on Participation	Source of Compensation
On-duty	May participate in research during work or duty hours with supervisor approval and no compensation other than $50 per blood draw	Federal or non-federal source
Off-duty	No restrictions in participation	Non-federal source only (except compensation for up to $50 per blood draw

		can be from a federal source)

There are no restrictions regarding on or off-duty participation or compensation source for subjects who are not DoD-affiliated personnel.

d. Medical Care for Research Related Injury.

(1) Federal regulations governing human subjects research require that research subjects involved in GTMR research must be informed about the availability of medical treatment or compensation if a research-related injury occurs. This information should include whether treatment is available, and if it is, what it consists of or where further information may be obtained (32 CFR 219.116/21 CFR 50.25). All non-exempt research reviewed by the HQ MRDC IRB must meet this minimum standard.

(2) The HQ MRDC IRB will ensure that DoD-conducted and DoD collaborative research also meets the requirements specified in DoDI 3216.02 Section 3.12 to protect human subjects from medical expenses that are the direct result of participating in DoD-conducted greater than minimal risk research.

(3) Research conducted by MRDC subordinate commands must also comply with MRDC Command Policy "Medical Care for Research-Related Injury in Human Research Conducted by the MRDC," that specifies the following language for consent documents:

If you are injured because of your participation in this research and you are a DoD healthcare beneficiary (e.g., active duty military, dependent of active duty military, retiree), you are entitled to medical care for your injury within the DoD healthcare system, as long as you remain a DoD healthcare beneficiary.

If you are injured because of your participation in this research and you are not a DoD healthcare beneficiary, you are entitled to care for your injury at DoD hospitals or clinics, but care for your injury may be limited to a given time period, and your insurance may be billed. It cannot be determined in advance which DoD hospital or clinic will provide care. If you obtain care for research-related injuries outside of a DoD hospital or clinic, you or your insurance will be responsible for medical expenses.

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

(4) Subjects participating in research under the HQ MRDC IRB's purview and conducted by DoD institutions can receive care in DoD MTFs as described under DoDI 6025.23, "Health Care Eligibility Under the Secretarial Designee Program and Related Special Authorities." Section 4.i. states:

Research subjects are eligible for health care services from medical treatment facilities (MTFs) to the extent DoD Components are required by DoDI 3216.02 to establish procedures to protect subjects from medical expenses that are a direct result of participation in the research;

Such care is on a non-reimbursable basis and limited to research injuries;

Care is authorized during the pendency of the volunteer's involvement in the research, and may be extended further upon the approval of the USD(P&R). (Note: "Pendency" means the period while the research project is continuing and the subject's involvement is continuing)

Verbiage as in paragraph (3), but omitting reference to DoD hospitals or clinics, will be substituted for these institutions' consent documents.

e. Volunteer Registry Management System (VRMS). USAMRDC maintains a database system that permits the identification of volunteers who have participated in GTMR research conducted by the USAMRDC or where an OTSG-sponsored investigational product is administered. On 12 January 2021, The US Army Surgeon General (TSG), granted USAMRDC's request for an exception from the requirements of Army Regulation 70-25 to maintain a registry of research volunteers; this exception allowed OHARO to cease accrual of new volunteer information into the existing VRMS. Upon study completion of ongoing research studies collecting VRMS datasheets, the institution's regulatory office will verify the submission of completed VRMS datasheets to the MRDC OHARO.

9-10. Posting of Clinical Trial Consent Form

a. The 2018 Common Rule includes a requirement for the posting of one IRB-approved consent form to a publicly available Federal website for each clinical trial conducted or supported by a Common Rule department or agency. Posting of IRB-approved consent forms is be done after the clinical trial is closed to recruitment, and no later than 60 days after the last study visit by any subject.

b. This requirement must be satisfied by an awardee institution. If the Federal department or agency supporting or conducting the clinical trial determines that certain information are not required to be made publicly available on a Federal website (e.g., confidential commercial information), the department or agency may permit the awardee to make redactions to the information posted. Until further DOD and/or other federal guidance or instructions regarding the implementation of this requirement is available, when the institution relying on the IRB is the prime awardee or supported institution for a clinical trial, the relying investigator should consult with the sponsoring program or grant officer on the award regarding how to satisfy this posting requirement, and maintain documentation of that communication and posting instructions.

Chapter 10. Special Populations

This chapter describes the HQ MRDC IRB's policies and procedures for the review and approval of research with (1) pregnant women and fetuses; (2) children; (3) individuals with impaired decision-making capacity; and (4) Service Members.

10-1. 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 MRDC 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 MRDC 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 MRDC 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.

10-2. Research with Pregnant Women and Fetuses

a. Research involving women who are or may become pregnant receives special consideration by the HQ MRDC 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 subjects 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 MRDC 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 pregnant subjects' exclusion from the research, or their separate study. However, while pregnant subjects are considered vulnerable subjects, 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 MRDC IRB considers the provisions of 45 CFR 46, Subpart B as follows when reviewing research with pregnant women as subjects. Per DoDI 3216.02, applicability of Subpart B is limited to research involving pregnant women as human subjects involved in research that is more than minimal risk and includes interventions or invasive procedures to the woman or the fetus; or fetus or neonate as human subjects.

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 as described in Chapter 9 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 9 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 9 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 MRDC 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 LAR is obtained in accord with the provisions described in Chapter 9 of this document, except that the consent of the father or his LAR 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 9 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 LAR 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 MRDC 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 MRDC 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.

(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.

10-3. 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 Subpart D, 45 CFR 46.401 - .408, (and 21 CFR 50.50 - .56 for FDA-regulated research) as follows. The HQ MRDC IRB may approve research involving children only if these special provisions are met.

(1) When reviewing research involving children, the HQ MRDC IRB classifies the research into one of four categories and documents the discussion 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 46.404/21 CFR 50.51). When the HQ MRDC 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 46.405/21 CFR 50.52). If the HQ MRDC 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 46.406/21 CFR 50.53). If the HQ MRDC 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 subjects 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 subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' 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.

Note: the additional requirements of 10 USC 980 would typically prevent DoD-supported or conducted research from being approvable under the provisions of 45 CFR 46.406/21 CFR 50.53.

(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 46.407/21 CFR 50.54). If the HQ MRDC 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 ASD,R&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 50.51, 50.52, or 50.53); 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 MRDC IRB must determine if the proposed study holds the prospect of direct benefit for subjects and document their discussions of the potential benefits of the research study as it relates to the requirements of Subpart D and 10 USC 980. The HQ MRDC 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 46.408/21 CFR 50.55, the HQ MRDC IRB must find and document that adequate provisions are made for soliciting the assent of some or all child subjects when in the judgment of the IRB some or all of the children are capable of providing assent.

(a) In determining whether children are capable of assenting, the HQ MRDC 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 MRDC 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 MRDC 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, 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 MRDC IRB determines that the child subjects 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 9 of this document regarding waiver or alteration of informed consent generally.

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

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 subjects 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 MRDC IRB determines that a research protocol is designed for conditions or for a subject population for which parental or LAR permission is not a reasonable requirement to protect the subjects (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 subjects, 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 subjects under the provisions described in Chapter 9 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.

10-4. Research with Individuals with Impaired Decision-Making Capacity

a. Persons with impaired decision-making capacity have diminished autonomy and special vulnerability as research subjects. To safeguard their interests and to protect these subjects from harm, the HQ MRDC IRB applies special ethical and regulatory considerations when reviewing research involving this population.

b. For subjects where there is the potential for cognitive impairment, the HQ MRDC 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' LARs may grant permission on their behalf for participation in research. Family members and close friends are not considered LARs 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 Individuals with Impaired Decision-Making Capacity

(1) LARs may grant permission for subjects who are unable to provide voluntary informed consent to take part in research. The 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 9). As noted previously, the HQ MRDC IRB will consider whether the 10 USC 980 requirements for all subjects to have the potential to benefit from the participation in the study are met.

(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 MRDC 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. Additionally, the HQ MRDC IRB considers whether and when to require reassessment of decision-making capacity.

(3) The HQ MRDC 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 MRDC 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 MRDC 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.

10-5. Research Involving Service Members

a. Service Members may be under unique constraints compared to other research subjects, 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 Service Members from research harms, special ethical and regulatory considerations may apply for reviewing research involving military personnel. The HQ MRDC IRB will consider the applicability of the following special provisions:

(1) The HQ MRDC IRB must find that research involving Service Members as subjects addresses additional applicable considerations as determined by DoD, Army, MRDC, and any local regulations.

(2) For research involving Service Members, the HQ MRDC 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 MRDC IRB will consider the following criteria during review of protocols that target enrollment of Service Members:

(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 Service 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 subjects are fair and immune from arbitrary intervention by personnel in the Service Members' chain of command;

(d) The research procedures or outcomes will not adversely affect Service Members' deployability during or after study completion; and

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

(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 Service Members as research subjects that will be considered by the HQ MRDC IRB include those described in Chapter 9 of this document regarding the requirement for an ombudsman, reducing undue influence by the chain of command, and payment for study participation.

Chapter 11. The Health Insurance Portability and Accountability Act (HIPAA)

11-1. Background and Definitions

a. The HIPAA was enacted by the US 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.

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

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

g. Use of PHI. Querying, viewing, and/or extracting any PHI, including for research purposes, within the covered entity.

h. 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.

i. 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.

j. 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.

k. Anonymous Data. Information collected or previously recorded without any of the 18 identifiers as defined by HIPAA and without assignment of a code that would allow data to be traced to an individual.

l. 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.

m. 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. The Privacy Rule permits covered entities to determine that health information is de-identified even if the health information 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.

n. 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 subject's medical record are not likely to be a part of the designated record set.

o. Data Use Agreement. An agreement between the covered entity and the recipient of a limited data set. This agreement establishes who is permitted to use or receive a 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.

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

q. Activities Preparatory to Research. An 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. This provision permits covered entities to use or disclose PHI without an individual's Authorization, a waiver or an alteration of Authorization, or a data use agreement.

11-2. HQ MRDC IRB Review of HIPAA Authorizations, Waivers, and Alterations

a. The HQ MRDC IRB may serve upon agreement, as a Privacy Board and review HIPAA Authorizations and review and approve requests for waivers or alterations of HIPAA Authorization for institutions relying on the HQ MRDC IRB. When the research requires a HIPAA determination (i.e., waivers or alterations of the requirement for HIPAA authorization), the review of the research for compliance with HIPAA regulations will be conducted by the IRB Chair, Vice-Chair, or by a designated expedited reviewer. HIPAA determinations may be made using expedited review procedures.

b. Research Use or Disclosure of PHI with Authorization. A Principal Investigator must obtain an Authorization from all subjects 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 LAR) 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 MRDC 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 MRDC 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 MRDC IRB waiver of Authorization.

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

(a) Statistical Method: The HQ MRDC 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. Subject'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. Subject'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 researcher may use or disclose PHI without HQ MRDC IRB review for the development of a research protocol, provided that all of the following criteria are satisfied and the Principal Investigator makes the required representations to the covered entity:

(1) The use or disclosure of PHI is solely to prepare a research protocol, or to identify prospective research subjects 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.

Researchers may include the necessary representations within the research protocol document.

i. Use and Disclosure of Decedent's PHI Without Authorization. A Principal Investigator may use and disclose decedents' PHI for research purposes without HQ MRDC 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 12. Food and Drug Administration-Regulated Test Articles

This chapter addresses the HQ MRDC IRB's role in review of research use of FDA-regulated products and non-research use of FDA-regulated products (including emergency use and humanitarian use devices).

The FDA is the Federal oversight agency responsible for protecting the public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, the nation's food supply, cosmetics, and products that emit radiation. The FDA is also responsible for advancing the public health by helping to speed innovations that make medicines and foods more effective, safer, and more affordable; and helping the public get the accurate, science-based information they need to use medicines and foods to improve their health. The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market, and then monitoring these products for continued safety.

12-1. Research Involving Investigational FDA-Regulated Test Articles

a. Overview.

(1) A test article is any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act (21 CFR 56.102(l)). FDA-regulated test articles include:

(a) Products that are not generally recognized as being safe and effective for any use under the conditions prescribed, recommended, or suggested by the FDA; and

(b) Products already approved by the FDA as safe and effective for specific indications that are being studied for new indications (or doses, strengths, or frequency) other than those that have been approved.

(2) When research studies submitted to the HQ MRDC IRB involve investigational or unlicensed test articles, the HQ MRDC IRB confirms that the uses of the test articles have appropriate regulatory approval or meet exemptions for such approval. To ensure review under the appropriate regulatory framework takes place, the OHARO IRB Office and HQ MRDC IRB review all submitted projects to identify whether protocols are subject to the FDA regulations (using the 2014 drug and device algorithms as needed). When applicability of the FDA regulations for a given protocol is unclear, the OHARO IRB Office consults the Office of Regulated Activities (ORA) for a written determination that is presented to the HQ MRDC IRB to ensure review under the appropriate regulatory framework takes place.

(3) For all research studies (clinical investigations) subject to 21 CFR 312 or 21 CFR 812, the HQ MRDC IRB reviews for compliance with the regulations at 21 CFR 312 or 21 CFR 812, 21 CFR 50, 21 CFR 56, as well as 32 CFR 219 and DoDI 3216.02. Where the FDA regulations and 32 CFR 219 differ, the HQ MRDC IRB ensures protocol compliance with the more restrictive regulation.

(4) Research with FDA-regulated test articles requires that the IRB has approved the protocol and the IRB:

(a) Receives documentation that the research will be conducted under an applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); or

(b) Formally determines and documents that the proposed use of an investigational device satisfies the FDA criteria for non-significant risk device research and reviews under the abbreviated IDE requirements; or

(c) Formally determines that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.

(5) In accordance with 21 CFR 56.106(a)-(e), the HQ MRDC IRB maintains IRB registration with the DHHS OHRP (IRB registration number IRB00007718). The HQ MRDC IRB revises its registration information by submitting changes to the OHRP website when necessary, and renews it registration every three years.

b. Research with Drugs

(1) Clinical investigations of drugs are subject to the IND regulations at 21 CFR 312. An IND is synonymous with a "Notice of Claimed Investigational Exemption for a New Drug." An investigational drug must have an IND in place with the FDA before it can be shipped, unless one of the exemptions specified in 21 CFR 312.2 (see below) is met.

(2) Protocol submissions for research on the use of a drug (unless that research is exempt from the IND regulations) must be accompanied by documentation from the FDA that includes a valid IND number. The IND number must either match the number on the sponsor protocol with the same title as the proposed research, or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IND numbers may not be validated with an Investigator Brochure (which may serve multiple INDs).

(3) As per 21 CFR 312.2(b), clinical investigation of a drug is exempt from the IND regulations if the drug is lawfully marketed in the United States and all of the following are true:

(a) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;

(b) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;

(c) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

(d) The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50; and

(e) The investigation is conducted in compliance with the requirements of 21 CFR 312.8 (Promotion and charging for investigational drugs).

(4) Additionally, a clinical investigation involving use of a placebo is exempt from the requirements of 21 CFR 312 if the investigation does not otherwise require submission of an IND.

(5) Clinical investigations that are exempt from IND regulations still require IRB review and approval, and as noted in paragraph iv above, are subject to the requirements of 21 CFR 50 and 21 CFR 56.

c. Research with Medical Devices

(1) Clinical investigations of medical devices are subject to the IDE regulations at 21 CFR 812. An approved IDE permits a device that is not approved (via premarket authorization (PMA)) or cleared to market (via 510(k)) by the FDA ,to be shipped to conduct clinical investigations of that device. Significant risk (SR) investigational devices must have an IDE approved by FDA before they can be shipped. Nonsignificant risk (NSR) devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a nonsignificant risk device.

(2) Medical device research falls into three categories:

(a) Investigations of SR devices to determine safety and effectiveness of the device.

(b) Investigations of NSR risk devices to determine safety and effectiveness of the device.

(c) Investigations exempted from the IDE regulations.

(3) Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research and/or where the research does not assess the safety or effectiveness of the device, are generally not considered to be FDA-regulated research and are therefore not subject to 21 CFR 812.

(4) SR and NSR Device Research

(a) When research is conducted to determine the safety or effectiveness of a device, the HQ MRDC IRB makes a SR or NSR device study determination by reviewing relevant information at a convened meeting. This information includes the description of the device, reports of prior investigations conducted with the device, the proposed investigational plan, and subject selection criteria. Studies proposed for review under the abbreviated requirements must comply with 21 CFR 812.2(b) as follows.

Abbreviated requirements. The following categories of investigations are considered to have approved applications for IDEs, unless FDA has notified a sponsor under 21 CFR 812.20(a) that approval of an application is required:

(1) An investigation of a device other than a significant risk device, if the device is not a banned device and the sponsor:

(i) Labels the device in accordance with 21 CFR 812.5; [i.e., “CAUTION--Investigational device. Limited by Federal (or United States) law to investigational use.”]

(ii) Obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;

(iii) Ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, informed consent under part 50 and documents it, unless documentation is waived by an IRB under 21 CFR 56.109(c).

(iv) Complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;

(v) Maintains the records required under 812.140(b) (4) and (5) and makes the reports required under 812.150(b) (1) through (3) and (5) through (10);

(vi) Ensures that participating investigators maintain the records required by 812.140(a)(3)(i) and make the reports required under 812.150(a) (1), (2), (5), and (7); and

(vii) Complies with the prohibitions in 812.7 against promotion and other practices.

(b) In addition to the sponsor's explanation of why the device is not a SR device, the HQ MRDC IRB considers the following during its review for SR/NSR determinations, and documents its determination in the meeting minutes:

1. The basis for the risk determination. The IRB will make the risk determination based on the proposed use of a device in the investigation, and not on the device alone.

2. The nature of harm that may result from use of the device. SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject and is either (i) intended as an implant, (ii) used in supporting or sustaining human life, or (iii) of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health.

3. Whether the subjects will need to undergo an additional procedure as part of the investigational study, for example, a surgical procedure. The HQ MRDC IRB will consider the potential harm the procedure could cause as well as the potential harm caused by the device.

(c) The HQ MRDC IRB will make the SR/NSR determination before it conducts its review of the study under the approval criteria in 21 CFR 56. The IRB will base its judgment about whether a study poses a SR or NSR on the significance of the potential harm that may result from participation in the study, including the use of the device; whereas the IRB will base its decision to approve a study for implementation on the study's risk-benefit assessment.

(d) The HQ MRDC IRB may agree or disagree with the sponsor's initial NSR assessment. If the IRB determines a study is NSR, it may approve the study if it meets all approval criteria; the study may begin without submission of an IDE application to FDA. If the IRB disagrees with the sponsor's NSR assessment, the HQ MRDC IRB will inform the Principal Investigator, who will notify the sponsor. SR device studies require submission to the FDA for approval of an IDE application.

(5) Exempted Investigations.

Clinical investigations that are exempt from IDE regulations still require IRB review and approval. The HQ MRDC IRB will assess device studies to determine if they comprise an exempted

investigation. Exempted investigations remain subject to the requirements of 21 CFR 50 and 56. An investigation of a medical device in human subjects research that is exempt from the IDE regulations must fall into one of the following categories (21 CFR 812.2(c)).

(a) A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.

(b) A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

(c) A diagnostic device, if the testing: is noninvasive; does not require an invasive sampling procedure that presents significant risk; does not by design or intention introduce energy into a subject; and is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.

(d) A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.

(e) A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

12-2. The HQ MRDC IRB's Role in Review of Non-Research Uses of FDA-Regulated Investigational Products: Expanded Access to Investigational Products for Treatment Use

The FDA regulations and guidance outline the requirements under which limited-availability medical products, to include investigational drug and device products, can be used to treat patients who: (1) are not otherwise eligible to participate in a clinical trial of the investigational product, and (2) have a serious disease or condition when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition.

The HQ MRDC IRB plays a significant role in the review of non-research use of investigational products in support of the DoD Force Health Protection program, as well as for Army Medical Treatment Facilities which may require emergency use of investigational drugs and devices (e.g., the US Army Institute of Surgical Research's Burn Intensive Care Unit, and the Landstuhl Regional Medical Center).

a. Treatment Use of Investigational Drugs.

The FDA permits expanded access to INDs for treatment use under the conditions described in 21 CFR 312, Subpart I. The FDA determines under which expanded access provision the investigational drug may be used: individual patients, including for emergency use (21 CFR 312.310); intermediate-size patient populations (21 CFR 312.315); or treatment IND or treatment protocol (21 CFR 312.320) for widespread use.

(1) Force Health Protection (FHP). The process for review and approval of DoD treatment (contingency) IND protocols for the purposes of FHP under the expanded access provisions is implemented by DoDI 6200.02. The USAMMDA FHP Division manages a portfolio of treatment protocols addressing preventive or therapeutic treatment designed to meet the anticipated or potential needs of Service Members and others. These unapproved products receive designation and approval by ASD, Health Affairs for FHP program use, and require approval by the HQ MRDC IRB. The treatment protocols are subject to the FDA regulatory and DoDI 6200.02 requirements but are not human subjects research and therefore are not subject to 32 CFR 219 or DoDI 3216.02 requirements. A number of these protocols allow for the possibility of administration of the product under 21 CFR 50.23 (a, b), exception from the general requirements for informed consent.

The OHARO IRB Office and HQ MRDC IRB work closely with the USAMMDA FHP Division to ensure appropriate IRB review, approval, and oversight of the portfolio of FHP treatment INDs. See Chapter 16 for additional information regarding the HQ MRDC IRB review of these protocols.

(2) Individual Patients, Including Emergency Use of Investigational Drugs (21 CFR 312.310). The FDA regulations provide for limited emergency use exception to the rules requiring an IND protocol's approval by the IRB. (21 CFR 56.104(c) and 21 CFR 56.102(d)).

FDA regulations do not allow for expedited IRB approval in emergency situations. However, an exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug or device on a one-time basis per institution without prior IRB review and approval if certain circumstances exist, and provided that such emergency use is reported to the IRB within five (5) working days. Any subsequent use of the IND product at the institution is subject to prospective IRB review and approval. However, the FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is that the IRB has not had sufficient time to convene a meeting to review the issue. The physician (referred to as an *investigator* in the FDA regulations) must obtain the informed consent of the patient or legally authorized representative for such an emergency use, except as described in Section 11-2.c below. The following conditions must be met for this type of emergency use: (a) a patient is in a life-threatening situation; (b) no standard acceptable alternative for treating the patient is available; (c) there is not sufficient time to obtain IRB approval.

(a) Criteria for Emergency Use. Emergency use must meet the definition above and the FDA must determine: [21 CFR 312.305(a)]

(i) The patient . . . to be treated has a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;

(ii) The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and

(iii) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.

Immediately life-threatening disease or condition means a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition means a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

The following must also be determined: [21 CFR 312.310(a)]

(i) The physician must determine that the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition;

(ii) FDA must determine that the patient cannot obtain the drug under another IND or protocol.

(b) In situations where prospective HQ MRDC IRB approval is not feasible, FDA regulations require the investigator to report the emergency use of an IND product to the IRB within five (5) working days of its use. See HQ MRDC IRB Guidance Document for institutions and physicians, “Emergency Use of Investigational Drugs and Biologics” for additional information and procedures.

b. Treatment Use of Investigational Devices.

(1) Emergency Use of Investigational Devices. A physician (investigator) who intends to treat a patient with an unapproved medical device in an emergency situation must conclude that:

(i) The patient has a life-threatening condition that requires immediate treatment;

(ii) No generally acceptable alternative treatment for the condition exists; and

(iii) Because of the immediate need to use the device, there is no time to use existing procedures to obtain FDA approval for the use.

An immediately life-threatening disease means a stage of a disease in which there is a reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

The investigator will make the determination that the patient’s circumstances meet the above criteria, assess the potential for benefit from the use of the unapproved device, and have substantial reason to believe that benefits will exist. In the event that a device is used in circumstances meeting the criteria listed above, the investigator should follow as many patient protection procedures as possible. Such patient protection procedures include obtaining:

(a) Informed consent from the patient or a legal representative, unless excepted via 21 CFR 50.23(a) (see next section);

(b) Clearance from the institution as specified by their policies;

(c) Concurrence of the HQ MRDC IRB Chair or Vice Chair;

(d) An independent assessment from a physician; and

(e) Authorization from the IDE sponsor, if an IDE exists for the device.

After the emergency use occurs, the investigator is responsible for ensuring that certain follow-up procedures occur. If an IDE exists for the device, the physician should provide the IDE sponsor with sufficient patient follow-up information to allow the sponsor to comply with the reporting requirements of the IDE regulation (i.e., within 5 working days after learning of the use). If no IDE exists, the investigator should submit a follow-up report on the use of the device to the FDA IDE staff within 5 working days after use. This report should contain a summary of the conditions constituting the emergency, patient protection measures that were followed, and patient outcome information.

(2) Compassionate Use (Single Patient/Small Group Access). The compassionate use provision allows access for patients who do not meet the requirements for inclusion in a clinical investigation but for whom the treating physician believes the device may provide a benefit in treating and/or diagnosing their serious disease or condition when there is no satisfactory alternative. This provision is typically approved for individual patients but may be approved to treat a small group.

A physician interested in treating a patient under this provision first requests authorization from the sponsor. If the request is approved, the sponsor must obtain prior FDA approval before the patient may be treated. The IDE supplement requests approval for a protocol deviation under 21 CFR 812.35(a) and must include the following information:

(a) the patient's condition and the circumstances necessitating treatment;

(b) discussion of why alternative therapies are unsatisfactory;

(c) discussion of why the probable risk of using the investigational device is no greater than the probable risk from the disease or condition;

(d) identification of any deviations in the approved clinical protocol that may be needed in order to treat this patient; and

(e) the patient protection measures that will be followed (see Section 11-1(2)(a))

The treating physician is responsible for obtaining an independent assessment from an uninvolved physician, clearance from his/her institution, informed consent from the patient or LAR, and concurrence from the IRB chair. If the patient's condition allows, the HQ MRDC IRB will convene an *ad hoc* meeting to review the treatment protocol prior to the use of the investigational device. In specific instances, the FDA or sponsor may require prior review and approval by the IRB rather than concurrence from the IRB chair.

Following the compassionate use of the device, the physician must provide a summary of the use to the sponsor for submission to the FDA, and report any problems to the HQ MRDC IRB and the sponsor.

(3) Treatment IDE. An approved IDE specifies the maximum number of clinical sites and the maximum number of human subjects that may be enrolled in the study. During the course of the clinical trial, if the data suggests that the device is effective, then FDA may allow expansion of a trial to include additional patients with life-threatening or serious diseases when (a) The device is intended to treat or diagnose a serious or immediately life-threatening disease or condition; (b) There is no comparable or satisfactory alternative device or other therapy available to treat or diagnose that stage of the disease or condition in the intended patient population; (c) The device is under investigation in a controlled clinical trial for the same use under an approved IDE, or such clinical trials have been completed; (d) The sponsor of the investigation is actively pursuing marketing approval/clearance of the investigational device with due diligence. A physician who receives an investigational device for treatment use under a treatment IDE is an investigator under the IDE and is responsible for meeting all applicable investigator responsibilities under 21 CFR 812, 21 CFR 50, and 21 CFR 56, including prospective HQ MRDC IRB approval.

c. Exception From Informed Consent Requirement

An exception under the FDA regulations at 21 CFR 50.23 permits the use of a test article without informed consent where both the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

(1) The subject is confronted by a life-threatening situation necessitating the use of the test article;

(2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from the subject;

(3) Time is not sufficient to obtain consent from the subject's legally authorized representative; and

(4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If, in the investigator's opinion, immediate use of the investigational product is required and if time is not sufficient to obtain the independent physician determination, the investigator should make the determination and, within 5 working days after the use of the article, have the determination reviewed and evaluated in writing by an independent physician. Documentation of the above must be submitted to the HQ MRDC IRB within 5 working days after emergency use of the test article.

d. IRB Review Following Use of a Test Article Under Expanded Access Provisions

The HQ MRDC IRB Chair, Vice Chair, or designated IRB member will review all required documentation submissions. The review comprises an assessment of whether or not the relevant regulatory requirements were met. The OHARO IRB Office will prepare a memorandum for the IRB reviewer's signature documenting acceptance of the submitted materials to send to the investigator, sponsor, and institution. Alternatively, if concerns are identified, the HQ MRDC IRB Chair, Vice Chair, or designated IRB member may refer the action to the convened IRB for consideration of potential noncompliance. The OHARO IRB Office will maintain all relevant documentation in the IRB records.

e. Humanitarian Use Devices.

A humanitarian use device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. A humanitarian device exemption (HDE) is a PMA application, but is exempt from the effectiveness requirements of a PMA. A HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from the HUD's use, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. Additionally, the applicant must demonstrate that no comparable devices are available to treat or diagnose the disease or condition, and that they could not otherwise bring the device to market.

An approved HDE authorizes marketing of the HUD. However, the HUD may only be used after the HQ MRDC IRB has approved the use of the device to treat or diagnose the specific disease at a given institution. The labeling for a HUD must state that the device is a Humanitarian Use Device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

Physicians who want to study a HUD for a new indication must submit an IDE application to the FDA if the device is a significant risk device. Physicians may be either the sponsor or investigator of the study or they may want to involve the HDE holder as the sponsor. The investigational use of a HUD under these circumstances is a clinical investigation and must be conducted in accordance with 21 CFR 812, 50, 54, and 56.

(1) The HQ MRDC IRB has the following responsibilities related to the review of an effort involving a HUD:

(a) Approve the effort before the HUD can be used;

(b) Review the following materials during initial review of the HUD: (1) a copy of the HDE approval order; (2) a description of the device; (3) the product labeling; (4) information related to the patient information packet that may accompany the HUD; (5) a sample consent document for the use of the HUD; and (6) a summary of how the physician proposes to use the device, including a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures;

(c) Conduct initial review at convened IRB meeting;

(d) Review the submission based on a) criteria 21 CFR 56.111, specifically to review the risks to patients that are found in the product labeling, ensure the risks are minimized, and evaluate whether the risks are reasonable in relation to the proposed use of the device; b) verify that health care providers are qualified through training and expertise to use the device; c) require informed consent that is consistent with the approved labeling for use of the HUD; d) verify that the consent document states that effectiveness of device has not been demonstrated; e) verify that physicians distribute patient information packets that generally contain a discussion of the potential risks and benefits of the HUD and any procedures associated with use; f) verify that the HUD label states: "Authorized by Federal Law for use in the [treatment or diagnosis] of

[specific disease or condition]. The effectiveness of this device for this use has not been demonstrated;"

(e) May approve for general qualifying population, individuals meeting qualification, or on a case-by-case basis;

(f) May specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB, IRB Chair, appropriate follow-up precautions and evaluations, or any other criteria it determines to be appropriate;

(g) May require the Medical Device Reporting (MDR) to the FDA be submitted to the IRB;

(h) Request the HDE holder for copies of the safety information submitted to the FDA, and information that could have a bearing on human safety (this information would be considered at the time of continuing review);

(i) Conduct continuing review, which may be done under expedited review procedures, and consider the risk and benefit information available and any MDR reports, and safety information;

(j) Does not need to make the determination of a SR or NSR device of a HUD when used within its HDE-approved indication(s).

(2) HUD Emergency Use

If a physician in an emergency situation determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior HQ MRDC IRB approval. The physician must, within 5 days after the emergency use of the device, provide written notification of the use to the HQ MRDC IRB Chair. The written notification must include the identification of the patient involved, the date of the use, and the reason for the use.

Chapter 13. Research Using the Internet

a. The HQ MRDC 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 MRDC IRB will consider the risks to the subjects and determine if an appropriate level of protection exists.

(a) The IRB will consider that each communication carries the risk of a breach of confidentiality. Even when data are 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 subjects 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 MRDC IRB will consider all additional requirements outlined in Chapter 10.

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

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

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

(4) Because there is no standard for identifying distressed subjects online, the HQ MRDC IRB will take into consideration potential subject 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 Subject Recruitment.

(1) The HQ MRDC 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 13).

(2) There are a variety of listing services that post information about research opportunities for potential subjects. If this method is used in recruitment of potential subjects, the material submitted to the HQ MRDC 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 MRDC IRB, the intended use must be submitted as an amendment to the already approved protocol (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 subject 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 MRDC 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 MRDC IRB must review and approve information about its administration.

Chapter 14. Recruitment and Advertising

14-1. 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 subjects, under-representation of women, men, 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, researchers must design recruitment methods 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)

14-2. Review of Recruitment Methods and Advertisements

a. The HQ MRDC 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 subjects.

b. The HQ MRDC IRB will review proposed payments to subjects to determine that the amount, method and timing of payment will not have undue influence on subjects, e.g., credit for payment should accrue as the study progresses rather than being contingent upon subject completion, any completion bonus should be reasonable and not so large as to unduly induce subjects to stay in the study when they would otherwise have withdrawn. The IRB will ensure that all information concerning payment, including the amount and schedule of payments, is appropriately described in the consent document.

b. The HQ MRDC IRB considers advertising or soliciting for study subjects as 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 subjects following the HQ MRDC IRB's initial approval of the protocol, the advertising is considered an amendment to the ongoing study.

d. The HQ MRDC 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 recorded for broadcast, the HQ MRDC IRB must review the final audio or video recording. The HQ MRDC IRB may review and approve the wording of the advertisement prior to taping to preclude re-recording because of inappropriate wording.

e. The HQ MRDC IRB reviews recruitment methods and advertising to ensure that it is 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 subjects who are likely to be vulnerable to undue influence.

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

(2) Any advertisement used to recruit subjects should be limited to the information the prospective subjects 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 subjects; 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 a drug, biologic, device, or other type of research intervention is safe or effective for the purposes under investigation;

(b) Claims, either explicitly or implicitly, that a 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 by the FDA; or

(d) Promises of “free medical treatment,” when the intent is only to say that subjects will not be charged for taking part in the investigation.

f. Additional recruitment requirements:

(1) Telephone Screening. The first contact prospective study subjects may have is with a study team member on the telephone. A script used to discuss or screen potential subjects to determine basic eligibility for the specific study is often used. The HQ MRDC IRB must review the procedures and scripts used to ensure that they adequately protect the rights and welfare of the prospective subjects. Additionally, the IRB will evaluate any information collected about prospective subjects 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 MRDC 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) clinical trials listing (ACTIS), and the National

Institutes of Health (NIH) listing at clinicaltrials.gov. For other Internet recruitment sites, HQ MRDC IRB review and approval is required prior to implementation.

(3) Mass Communication E-mails. Advertising transmitted through mass email solicitation must be reviewed and approved by the HQ MRDC 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). Consideration should be given to the source of the email solicitation within an organization to avoid undue influence or coercion, e.g., by superiors in the target population's chain of command.

(4) Recruitment Using Databases and Health Care Providers. Investigators may request to use search methods of particular databases to identify potential subjects that may be eligible for research projects (e.g., search by disease, age, gender, etc.), or they may request to contact health care providers for access to potential subjects from the provider's patient population. Such recruitment methods require HQ MRDC IRB approval prior to initiation (unless the recruitment method meets the criteria as an "activity preparatory to research" as described in Chapter 11).

(5) Screening, recruiting, or determining the eligibility of prospective subjects for inclusion in the research does not require investigators to obtain a waiver of consent.

(a) The HQ, MRDC IRB will approve a research study in which an investigator will obtain information or biospecimens for these purposes without the informed consent of the prospective subject or the subject's LAR if either of the following conditions is met:

(1) The investigator will obtain information through oral or written communication with the prospective subject or LAR, or

(2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

(b) The research protocol must describe the activities involved in the screening and recruiting process. HIPAA requirements will continue to apply, when applicable. It is also necessary to obtain consent, or a waiver of consent, before involving a subject (including the use of their identifiable private information or biospecimens) in other research activities.

Chapter 15. 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 OHARO IRB Office prior to initiation of the study. The OHARO 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 OHARO 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 MRDC IRB review (see Chapter 6).

b. The OHARO IRB Office's review includes assessing the source of previously obtained specimens or data and whether the initial manner and consent for the specimens or data collection permits use in the proposed research protocol. The OHARO IRB Office or HQ MRDC IRB will review the use of previously obtained specimens or data for a new research purpose to ensure the use is consistent with the originally approved protocol and consistent with the expectations of the specimen/data donor, e.g., 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 are not 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 OHARO 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 MRDC 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 release of specimens and/or data.

(4) The OHARO IRB Office and HQ MRDC 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 MRDC IRB approval to do so.

Chapter 16. HQ MRDC IRB Review of Force Health Protection Treatment Protocols Under DoDI 6200.02

a. Background. 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. DoDI 6200.02 designates the MRDC Human Subjects Research Review Board (now the HQ MRDC IRB) as the single IRB for review and approval of the DoD treatment IND protocols for FHP. These protocols undergo initial and continuing IRB review and approval, and are available for implementation when/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 in the relevant excerpts 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 USC. 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 MRDC IRB in the Review of Treatment IND protocols for FHP. Paragraph E4.4 of DoDI 6200.02 designates the HQ MRDC IRB as the IRB responsible for review the treatment 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 generally acceptable. All locally modified documents must be submitted to the HQ MRDC 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 Defense for Health Affairs, develop a specific treatment protocol for use of the IND. The protocol is approved by the HQ MRDC IRB as a duly constituted IRB under 21 CFR 56. The HQ MRDC IRB considers the protocol for compliance with the requirements found in 21 CFR 50 and other applicable FDA regulations. *Note that the requirements of 32 CFR 219 and DoDI 3216.02 do not apply to FHP protocols.* The only exceptions to DoDI 6200.02 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 MRDC 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 MRDC 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 USC. 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 USC. 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 USC. 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 MRDC IRB will review and, if appropriate, will approve the requested protocol with a waiver of informed consent. As with any other protocol, HQ MRDC 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 of the need to inform; and, in fact, the regulation focuses on the information provided to both Service Members and health care providers. The HQ MRDC 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 subjects. Finally, the HQ MRDC IRB will review the adequacy and plans for providing information to health care providers.

Upon review and approval by the HQ MRDC IRB of a request for using a product with a waiver of informed consent under 21 CFR 50.23(d), the minutes of the HQ MRDC 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 17. Protocol Life Cycle Issues: Amendments, Continuing Review, and Closure

17-1. Amendments

a. 32 CFR 219.108(3)(iii)/21 CFR 56.108(a) require 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 MRDC 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 the revised protocol and any other revised study documents, 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. If the modification of the protocol significantly impacts the study design, methodology, data analyses, etc., the institution or the HQ MRDC IRB may require scientific review of the proposed changes.

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.

f. Minor Modifications to Research Eligible for Expedited Review. Minor modifications to a study that was reviewed by full Board may be reviewed and approved by the expedited review procedure (see 32 CFR 219/21 CFR 56.110(b)(2)). See Chapter 7-6 for additional information and common examples.

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 subjects, 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 in advance 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.

(1) A request for a protocol exception must be reviewed and approved by the HQ MRDC IRB (either by expedited or convened IRB procedure as noted in paragraphs e, f, and g above) 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 MRDC 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, or disapprove the protocol exception.

(4) The Investigator will maintain documentation of sponsor (or FDA) approval and HQ MRDC IRB approval of the exception in the Investigator's research study file.

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

i. During review of an amendment or exception request, the IRB will determine whether any significant new findings that might relate to subjects' willingness to continue participation should be provided to subjects.

j. Instituting Unapproved Changes in Approved Research. Implementing unapproved changes in a HQ MRDC IRB-approved protocol (***except when necessary to eliminate apparent immediate hazards to the subject***) violates the requirements found at 32 CFR 219.108/21 CFR 56.108. If implementation of an unapproved change is suspected, OHARO IRB Office staff in coordination with the HQ MRDC IRB Chair and the research institution will investigate the matter and generate a report. The IRB will be provided with information about the violation, to include, at a minimum, the original report and any supporting documentation, 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 MRDC 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 19) and discuss appropriate sanctions and/or required re-training to prevent future non-compliance.

17-2. Continuing Review of Research

a. Research initially assessed by the IRB as presenting GTMR to subjects and research not conducted under an investigational new drug application or investigational device exemption where expedited review 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, requires at least annual IRB review and approval for continuation.

b. All FDA-regulated studies, regardless of whether the protocol was initially approved through expedited review procedures, also require at least annual IRB review and approval for continuation.

c. Continuing review will be required for protocols initially reviewed and approved by expedited procedure when it is required by the HQ MRDC IRB Chair, Vice Chair, or designated IRB expedited reviewer. The IRB must document the rationale for requiring continuing review in such cases. The IRB may determine that continuing review is required when:

(1) Required by other applicable regulations, e.g. FDA regulations (appropriate for a FDA-regulated study).

(2) The research involves topics, procedures, or data that may be considered sensitive or controversial.

(3) The research involves vulnerable subjects or circumstances that increase subjects' vulnerability.

(4) An investigator has minimal experience in research or the research type, topic, or procedures.

(5) An investigator has a history of noncompliance.

d. The review criteria for continuing review by the IRB are the same as for initial review.

e. The IRB Office will send courtesy reminders to Principal Investigators for the submission of continuing review reports 60-, 45-, and 30-days prior to IRB approval expiration, as needed. These submissions must arrive at the OHARO IRB Office at least 30 calendar days prior to the protocol’s IRB approval expiration date.

f. Elements of the Continuing Review Report.

(1) The Principal Investigator will prepare and submit a continuation report to the HQ MRDC IRB that summarizes the progress of the research.

(2) Pursuant to 32 CFR 219.108(b)(4) and 21 CFR 56.108(a) investigators must submit sufficient information for the IRB to consider re-approval of the research protocol. Investigators will complete the HQ MRDC IRB Continuation Report form and provide supporting documents to include the current version of the protocol and informed consent form(s) as applicable. The report must at a minimum include (a) a summary of the progress to date and findings obtained thus far; (b) the number of subjects accrued, withdrawn, or discontinued, and the reasons; (c) a summary of all unanticipated problems involving risks to subjects or others, AEs, deviations, and any complaints about the research; (d) a summary/synthesis of relevant recent literature and whether it may have an impact on the current research, a summary of all 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; (e) any statements of significant new findings provided to subjects, and a statement regarding any changes in potential conflicts of interest for the study team; (f) a list of current study team members and their human subjects protection training status, the current and any proposed new informed consent document, and the current Investigators' Brochure or Device Users' Manual, if there is one (for all IND and Investigational Device Exemption (IDE)) studies).

(3) Principal Investigators who become aware of any publications, safety monitoring reports, interim results, or other findings indicating a change to the study's risks or potential benefits during the reporting period should not delay informing the HQ MRDC IRB or making any necessary changes to the protocol until the continuing review report's due date.

(4) 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 remain 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.

g. Review Criteria for Continuing Review. The review of the protocol must be substantive and meaningful, and the review criteria for either expedited or full Board continuing review of human research protocols are the same as those for initial review (i.e., IAW 32 CFR 219/21 CFR 56.111). For convened reviews:

(1) In conducting continuing review of research not eligible for expedited review, the same primary reviewer system as for initial convened HQ MRDC IRB reviews will be employed as previously described. The OHARO 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 MRDC 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 MRDC 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.

h. Conditional Approval. Studies receiving conditional approval may continue while stipulations are addressed, unless the IRB specifies otherwise (e.g., all research activities must

stop until conditions are met; research activities with currently enrolled subjects may continue, but no new subjects may be enrolled until conditions are met). Delay in completion of any required modifications will not move the expiration date or extend the approval period.

i. Expired Approval.

(1) If a study is not re-approved by its expiration date, the OHARO IRB Office will immediately notify the Principal Investigator and the research institution, and all study activities must cease except for those activities required to prevent placing subjects at risk.

(2) Once a protocol's IRB approval expires, it must undergo review and approval by either expedited or full Board procedure 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 MRDC IRB. A new anniversary date for the protocol's expiration of IRB approval will be established based on the IRB's approval date.

(3) Once a protocol's IRB approval expires, the IRB Office will administratively close a protocol if the Principal Investigator does not 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 MRDC IRB within 10 business days after IRB approval expiration.

17-3 When Continuing Review is Not Required

a. All exempt protocols initially reviewed and approved by limited IRB review procedure are not reviewed for continuation by the HQ MRDC IRB. However, the IRB may determine that continuing review is required for a particular study subject to limited IRB review. In this case, the IRB will document the rationale for requiring continuing review in the IRB record and communicate the continuing review requirement to the requesting institution in the IRB determination letter.

b. All protocols initially reviewed and approved by expedited review procedure will not undergo continuing review.

c. Additionally, in accordance with 32 CFR 219.109(f), the requirement for continuing review of research **is not required** for research that has progressed to the point that it involves only one **or** both of the following, which are part of the IRB-approved study:

(1) Data analysis, including analysis of identifiable private information or identifiable biospecimens, **or**

(2) Accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

d. After the initial review and approval of proposed research involving human subjects, the HQ MRDC 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 remain

satisfied, namely, determinations as to the risks, potential benefits, adequate informed consent, and safeguards in the conduct of the protocol. The major issues for consideration 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 informed consent document is still accurate and complete and 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, e.g., whether any significant new findings that might relate to subjects' willingness to continue participation should be provided to subjects.

e. When CR is not required, the IRB Office will issue a periodic reminder to the investigator that the research remains under IRB oversight, and that the following be submitted to the IRB as applicable:

(1) Modifications made to the research or informed consent process/document(s);

(2) Prompt reporting of unanticipated problems involving risks to subjects or others, related and unexpected serious adverse events and/or unanticipated adverse device effects;

(3) Any protocol deviation that affects subjects' safety or rights and/or the integrity of the study will be promptly reported to the IRB;

(4) Any new conflicts of interest or changes in existing conflicts for the PI and research staff members, as applicable. This could include new financial interests with a research sponsor or new financial or other 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.

(5) A final study report and request to close the protocol upon completion of all research activities with human subjects or their identifiable data/biospecimens.

17-4 "Full-Board" Initial Review Followed by "Expedited" Continuing Review. The IRB awaits OHRP Guidance on Categories (8) and (9) in the Federal Register list of categories of research permit an IRB to conduct expedited continuing review. This policy will be modified to reflect OHRP guidance.

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

(1) 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

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

(3) 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.

(b) 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 by expedited procedure, subsequent to a full Board initial review, where the following three conditions are met:

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

(2) The IRB determines that research presents NGTMR to subjects; and

(3) No additional risks have been identified in research during the initial or subsequent approval periods.

*Note: the HQ MRDC IRB follows FDA opinion that NSR device studies are eligible for expedited review under Category (9), as no IDE application is required for NSR device studies conducted under the abbreviated IDE requirements in 21 CFR 812(b).

17-5. Protocol Closure/Final Study Report

a. One of the procedural requirements of an IRB (32 CFR 219.108(a)(3)) is ensuring "prompt reporting to the IRB of proposed 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 MRDC 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 means the end of subject recruitment and all subject interactions and the completion of all planned experiments, analyses, or manipulations of research materials. Any planned, contemplated, or potential uses of retained research materials not already specified and approved in a current project must be reviewed and approved as a new protocol.

d. When to Close a Research Protocol to MRDC IRB Oversight.

(1) For a protocol to be closed to continuing IRB review, it must meet the following criteria: (a) enrollment must be closed, (b) all subjects must have completed all research-related interventions, (c) all subjects must have completed all research-related follow-up, (d) data collection is complete and no further data collection will be conducted, and (e) analysis of already collected data is the only activity remaining, and the data are de-identified (i.e. there are no subject identifying codes or links to the data; those conducting data analysis cannot ascertain the subject's identity. Note: if the only remaining activity is analysis of de-identified data, the protocol may be closed to IRB oversight and the institution may reclassify the remaining activities as research not involving human subjects).

(2) Prior to conclusion of the study, the Principal Investigator must coordinate with the research monitor, if applicable, for any required medical follow-up and/or debriefing of volunteers. The Principal Investigator must also notify all research personnel of the closure of the protocol and that no further research activities are authorized. Principal Investigators need to be aware that once a protocol is closed to IRB review, it must be formally reopened only as a new protocol.

e. Three Distinct Closure Categories Defined by the OHARO IRB Office.

(1) Protocol Withdrawal. A study is defined as withdrawn from IRB review when the following situations occur:

(a) The Principal Investigator may request protocol withdrawal for reasons such as loss of funding, sponsor decision, change in available subject population, etc.

(b) The OHARO IRB Office may withdraw protocols from the IRB review process when the Principal Investigator fails to communicate or adequately respond to requests for information or documents, or provide complete responses to HQ MRDC IRB stipulations within 45 calendar days of initial IRB notification. The IRB Office will make at least two attempts to obtain a response prior to notifying the Principal Investigator and institution of the protocol's withdrawal.

(2) Protocol Termination. A study is defined as terminated if it is closed voluntarily or involuntarily by the Principal Investigator or the IRB following initiation of study procedures involving human subjects for reasons such as: (a) due to human subjects 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) when the Sponsor terminates the study ; 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) and the HQ MRDC IRB has accepted it.

Chapter 18. Reporting and IRB Review of Unanticipated Problems, Adverse Events, Deviations, when a Previously Enrolled Subject Becomes a Prisoner, and Knowledge of Pending Compliance Inspections

18-1. Reporting Requirements

a. 32 CFR 219.108/21 CFR 56.108 require 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 non-compliance 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 MRDC IRB are specified in the protocol document, “Principal Investigator Agreement: Responsibilities of the Principal Investigator in Human Research” that the Principal Investigator signs 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 its identification, but within five (5) business days of identification. It is acknowledged that although circumstances may prevent immediate notification of reportable events, all required reporting must occur without delay. Investigators should contact the OHARO IRB Office with any questions about the interpretation of what events require reporting to the IRB.

18-2. 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 such problems as administering the incorrect dose of a study drug; loss of control of research agents, subject data, or hazardous materials; psychological reactions; breach of confidentiality; economic risks; less than ideal results of treatment, etc.

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 (UADE) 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. The IRB is not required to receive AE reports other than those that are also 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, the 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)).

f. The events that require prompt reporting to the IRB are given at 32 CFR 219.108(a)(3)(iii), 32 CFR 219.108(a)(4), 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.

18-3. Definitions

a. UPIRTSOs are any incident, experience, or outcome that meets all of the following criteria:

(1) 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 population being studied;

(2) Related or possibly related to a subject's participation in the research; AND

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

b. Adverse events are any untoward or unfavorable medical occurrence in a subject, including any abnormal sign, symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research.

c. Unexpected adverse events are adverse events occurring in one or more subjects in a research protocol, the nature, severity, or frequency of which is not consistent with either:

(1) The known or foreseeable risk of adverse events associated with the procedures involved in the research that are described in (a) the protocol-related documents, such as the IRB-approved research protocol, any applicable Investigator Brochure, and the current IRB-approved informed consent document, and (b) other relevant sources of information, such as product labeling and package inserts; or

(2) The expected natural progression of any underlying disease, disorder, or condition of the subject(s) experiencing the adverse event and the subject's predisposing risk factor profile for the adverse event.

d. Serious adverse events are those that result in death, are life-threatening, result in inpatient hospitalization or prolongation of existing hospitalization, result in persistent disability or incapacity, result in congenital anomaly or birth defect; or, based on medical judgment, may jeopardize subjects' health and may require medical or surgical intervention.

18-4. UPIRTSO, UADE, SAE, and AE Reporting Responsibilities of the Principal Investigator to the HQ MRDC IRB

a. To fulfill the HQ MRDC IRB's responsibility for monitoring and oversight of research, all UPIRTSOs, UADEs, and SAEs that are unexpected and determined to be at least possibly related or definitely related to study participation must be promptly reported by telephone (301-

619-2165), by email (usarmy.detrick.medcom-usamrmc.other.irb-office@health.mil), or by facsimile (301-619-4165) to the OHARO IRB Office. A complete written report must follow the initial notification.

b. The Principal Investigator will assess AEs to determine whether the AE is an unanticipated problem requiring prompt reporting by answering the following questions:

(1) Is the AE unexpected?

(2) Is the AE related or possibly related to participation in the research?

(3) Is the AE serious or does the adverse event suggest that the research places subjects or others at a greater risk of harm than was previously known or recognized?

If the answer to **ALL** questions above is yes, then the AE may constitute a UPIRTSO and it requires prompt reporting to the HQ MRDC IRB.

c. For protocols with an assigned research monitor, the research monitor must review reports of SAEs/UPIRTSOs and provide an unbiased written report of the event. At a minimum, the research monitor should comment on the outcomes of the event or problem and the relationship to participation in the study. The research monitor should also indicate whether s/he concurs with the details of the report provided by the Investigator.

d. Unanticipated problems involving risks to others must also be reported (e.g., 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. The HQ MRDC IRB will assess the event and make a final determination regarding whether the event comprises a UPIRTSO.

Examples of UPIRTSOs include, but are not limited to:

(1) More frequent or severe side effects than were anticipated, as described in the protocol and consent document;

(2) The PI's computer, with subjects' personally identifiable private information, is stolen or misplaced, posing a risk to patient confidentiality (confidentiality may or may not be breached);

(3) Malfunctioning of research equipment that results or could result in risk to subjects or staff.

(4) A research technician suffers an inadvertent biological or chemical exposure during the study.

e. Based on the nature of the research (e.g., a novel study presenting GTMR), the HQ MRDC IRB may require additional prompt reporting of SAEs or AEs for a given research study. This means that based on factors such as (but not limited to) whether the research involves high risk to subjects, the amount of documentation available regarding potential risks, or whether the protocol involves novel procedures with unknown risks or hazards, the IRB may modify the baseline reporting requirements for a given research protocol (e.g., require the investigator to report all SAEs or all AEs of a particular nature). The HQ MRDC IRB will impose these

additional reporting requirements during the time of initial or continuing review as stipulations for revisions to the protocol.

f. In addition to the prompt reporting of UPIRTSOs and unexpected related SAEs, all UPIRTSOs and unexpected related SAEs occurring during the reporting period, as well as all AEs (serious and non-serious, related and unrelated, expected and unexpected) occurring during the reporting period must be described in the continuing review report submitted to the HQ MRDC IRB and summarized in the final report at the conclusion of the study.

g. Information regarding unexpected study-related SAEs or UPIRTSOs received from other sites on multi-site protocols should also be provided promptly by the Principal Investigator to the HQ MRDC IRB for review. The IRB Office will provide acknowledge of receipt and maintain the submitted reports in the official IRB file. An assessment from the PI or the Sponsor of the study of the causality of the event(s), the seriousness of the event(s), and whether or not the event(s) was expected must accompany the submission of these reports.

18-5. IRB Assessment of Reported UPIRTSOs

a. Upon receipt of a reported UPIRTSO (including UADEs and SAEs), the HQ MRDC IRB Chair or designee will assess the report to confirm that the event meets the criteria for prompt reporting to the HQ MRDC IRB. If the Chair or designee concurs with the Principal Investigator that an event is a possible UPIRTSO, then the report will be reviewed by the convened board.

b. IRB members will receive and consider the initial, follow-up, and research monitor's (as applicable) report in assessing reported events, as well as any other documents relevant to the assessment (typically the current protocol, ICD and IB or device manual if applicable). The IRB may request additional information from sources such as the Principal Investigator, study team, or institution in order to adequately determine whether an event constitutes a UPIRTSO.

c. Once the IRB makes a final determination that an event comprises a UPIRTSO, the IRB will consider a range of actions, including but not limited to suspending or terminating the protocol, requiring a protocol amendment, requiring re-consent of current subjects and/or informing past subjects.

d. Findings and recommendations by the HQ MRDC IRB related to a UPIRTSO determination will be communicated to the investigator and IO, as well as reported to the CG, MRDC and applicable agencies, as described in Chapter 22.

18-6. Deviations and Violations: Background

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 subject, investigator, or staff. Deviations include:

a. 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, or willingness to continue participation, or may affect the scientific design of the study and/or the integrity of the study or its resultant data. Major deviations should be promptly reported to the HQ MRDC IRB.

b. 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. Minor deviations must be reported to the HQ MRDC IRB at the time of continuing review.

c. Violations. A protocol violation is 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 study or its resultant data. Violations may also be repeated deviations (major or minor) of the same nature. Violations can represent serious or continuing noncompliance with the Federal regulations and guidelines for ethical conduct of human subject research.

d. 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 MRDC IRB prior to its implementation (See Section 16-1). The HQ MRDC IRB may require that the Principal Investigator consider amending the protocol if the IRB receives repeated requests for related/similar protocol exceptions.

18-7. Reporting Requirements for Major Deviations and Violations

a. Deviations that meet the definition of a major deviation, and all protocol violations, must be promptly reported to the HQ MRDC IRB 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 MRDC IRB a report that includes a description of the major protocol deviation(s)/violation, 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 require 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 MRDC 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, the HQ MRDC IRB must promptly review such changes following their occurrence.

d. The HQ MRDC IRB Chair, Vice Chair, or IRB member designee can review, assess, and accept the deviation or violation report and remediation plan or refer the report for review by the convened IRB.

e. The convened HQ MRDC IRB, or the Chair, Vice Chair or IRB member designee will determine whether a minor or major deviation occurred, and if the deviation may also comprise a UPIRTSO (see Chapter 18-4 above) or serious and/or continuing noncompliance (see Chapter 20). The convened HQ MRDC 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 IRB may place the protocol on hold or suspend it pending resolution or implementation of the IRB's requirements.

f. If it is necessary to make a permanent change to the study procedures in order to avoid harm to other subjects, then the Principal Investigator must submit an amendment to the protocol as soon as possible. If appropriate to maintain safety of the subjects, the Principal Investigator should temporarily stop new subject enrollment until the amendment is approved.

18-8. Reporting Requirements for Minor Deviations

Deviations that meet the definition of a minor deviation, and that are not recurring, should be reported to the HQ MRDC 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:

a. Routine lab work for a subject who has a history of previously normal lab values that was missed, but did not introduce any safety concerns for the subject;

b. Visit outside of study window that has no impact on the subject or study;

c. Study procedure conducted out of sequence.

18-9. Studies in Which a Previously Enrolled Subject Becomes a Prisoner

a. Principal Investigators must promptly notify the HQ MRDC IRB when a previously enrolled human subject becomes a prisoner and the research protocol was not reviewed and approved by the IRB in accordance with 45 CFR 46 Subpart C and DoDI 3216.02 requirements.

b. If the Principal Investigator asserts to the HQ MRDC IRB that it is in the best interest of the prisoner-subject to continue to participate in the research while a prisoner, the IRB Chair may determine that the prisoner-subject may continue to participate until the convened IRB can review the Principal Investigator's request to approve a change in the research protocol and until the research organization's IO and the OHARO review the IRB's approval to change the research protocol. Otherwise, the IRB Chair shall require that all research interactions and interventions with the prisoner-subject (including obtaining identifiable private information) cease until the convened IRB can review this request to approve a change in the research protocol.

c. Upon receipt of such notification, the HQ MRDC IRB will promptly convene to review the research protocol to ensure that the rights and well-being of the prisoner-subject are not in jeopardy. The IRB will identify and consult with a subject matter expert having the expertise of a prisoner representative. During review of the change in the study to allow the prisoner-subject to continue to participate in the research, the convened HQ MRDC IRB will consider whether:

(1) The prisoner-subject can continue to consent to participate and remains capable of meeting the research protocol requirements;

(2) The terms of the prisoner-subject's confinement does not inhibit the ethical conduct of the research; and

(3) There are any other significant issues preventing the research involving human subjects from continuing as approved,

If the HQ MRDC IRB approves, the approval is limited to the individual prisoner-subject and does not allow recruitment of prisoners as subjects.

18-10. Reporting Requirement for Notification of Planned or No-Notice Inspections of Research by Outside Government Agencies

As soon as a Principal Investigator or the institution's HPD learns of a planned or no-notice compliance inspection, site visit, or audit of a research study by another government agency, e.g., FDA, OHRP, etc., s/he should immediately inform the OHARO IRB Office by telephone (DSN 312-343-7801 or 301-619-7801) and email (usarmy.detrick.medcom-usamrmc.other.irb-office@health.mil).

Chapter 19. 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 7) and continuing review through life cycle reporting (See Chapters 17 and 18) are the primary mechanisms by which the IRB monitors research. This chapter describes additional means by which the HQ MRDC IRB fulfills its oversight and monitoring responsibilities.

19-1. Verification of Unapproved Changes in Approved Protocols

a. 32 CFR 219.103(b)(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 MRDC IRB's monitoring and oversight activities. The HQ MRDC 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 MRDC IRB.

(4) Protocols in which 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 identifies or potential conflicts of interest.

(6) Protocols in which issues have been raised by the research 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 such verification may be raised during a scheduled continuing review, review of safety or other updates, and at or in advance of any scheduled IRB meeting. The HQ MRDC 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, OHARO IRB Office staff will review the appropriate information and prepare a focused review summary for consideration.

c. If any indication exists that there may be a need for verification of study information by sources other than the investigators that no material changes have occurred since the previous IRB meeting, the assigned HSPS will refer the protocol to the HQ MRDC IRB Chair or designee for further evaluation by the IRB.

d. HQ MRDC 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 section 17-5 below); or (c) verification at specified intervals during the subsequent approval period.

e. If, as a result of verification efforts by the HQ MRDC IRB, unapproved significant changes are found to have been deliberately instituted, the IRB will pursue the matter as a case of noncompliance with the Federal requirements (See Chapter 20) and may require immediate suspension of IRB approval as a first step (See Chapter 21).

19-2. Not-for-cause Post-approval Compliance Monitoring

a. In addition to the measures described above, the HQ MRDC IRB conducts additional routine post-approval compliance monitoring activities on an ongoing basis. These will typically take the form of scheduled site visit assessments and study audits. The IRB may employ alternate means of compliance monitoring for remote research sites, e.g., desk audits or use of VTC.

b. As applicable, site visit assessments may include but are not limited to evaluation of: subject accountability; informed consent/assent processes; site regulatory administration; staff qualifications; protocol compliance; Principal Investigator Master File and subject records; data management; documentation practices; subject protection measures and adverse events; test article accountability; information gained from Principal Investigator, research staff, and subject interviews.

c. Site visit teams will include representatives from the OHARO IRB Office, and may be augmented by staff from the OHARO Human Research Protection Office. IRB members may also accompany the IRB Office team to gain familiarity with the institutions served by the HQ MRDC IRB and assist in site visit activities.

d. The IRB Director or Deputy Director and Director, OHARO will set the schedule for site visits during each upcoming Fiscal Year. The decision of where and how often to conduct not-for-cause post-approval compliance monitoring visits is based on such factors as the length of time since the last visit to an institution, risk level of protocols, whether the institution has recently implemented a new research program for which the IRB needs to gain familiarity, etc.

e. The IRB Director or Deputy Director will notify the Institutional Official and HPD at least six to eight weeks in advance of the site visit, and provide OHARO IRB Office audit checklists and other information to aid the site in preparation for the assessment. The OHARO IRB Office will randomly select a representative sample of open, active protocols for audit, to include both greater than minimal risk and minimal risk research studies, ensuring that no one investigator is chosen for more than one study audit. Based on audit findings during the site visit, the number of protocols audited may be increased or decreased as needed to fully evaluate regulatory compliance.

f. The site visit team will provide on-the-spot feedback and education to Principal Investigators and study teams during audit/assessment activities.

g. Checklists or other documentation will be completed for all audit activities. At the conclusion of the assessment, the site visit Lead will complete a detailed report that summarizes audit findings and any recommended or required corrective actions. The report will be provided

to the IO; HPD; HQ MRDC IRB; Director, OHARO; and CG, MRDC. Any required follow-up actions will be tracked to ensure timely resolution.

h. If the audit raises urgent safety or regulatory concerns, the site visit team will notify the IO, HPD, HQ MRDC IRB, and Director, OHARO, immediately to determine appropriate actions to protect human subjects.

19-3. "For Cause" (FC) 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 noncompliance.

b. A FC review by the OHARO IRB Office may include: review of study master file documents; review of subject file documents, assessment of record management; focused review of consent 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; and interviews with study subjects.

c. At the end of the visit, the findings of the audit team, with any recommended 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 audit team will notify the HQ MRDC IRB immediately to determine if a hold on new enrollment or study suspension is warranted pending further review of the audit report. Otherwise, the HQ MRDC IRB will be informed of any findings and any recommended corrective actions at the subsequent IRB meeting.

e. Upon review of the audit report, the HQ MRDC IRB may determine that additional actions are necessary. These actions could include but are not limited to suspension or termination of the research, training for the Principal Investigator and study personnel, or further investigation and consideration regarding serious and/or continuing noncompliance (see Chapter 20.)

19-4. 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 MRDC 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 MRDC 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 MRDC 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 MRDC 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 subjects 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 MRDC 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 MRDC 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.

Chapter 20. Serious or Continuing Noncompliance

This chapter describes the HQ MRDC IRB's role in investigating, determining, and reporting serious or continuing noncompliance. Research conducted by MRDC subordinate commands must also comply with MRDC Command Policy "Investigating, Managing and Reporting Noncompliance with Human Subjects Research Regulatory Requirements."

20-1. Investigating Allegations of Noncompliance

The HQ MRDC IRB defines noncompliance as failure of a person, group, or organization to act in accordance with a law, regulation, or policy governing human subjects research, the requirements and/or determinations of the overseeing IRB, or the research protocol.

Note: Research protocol noncompliance in the form of protocol deviations can be minor or major. Major protocol deviations may also comprise or constitute serious and/or continuing noncompliance as they may potentially adversely affect subjects' rights, welfare or willingness to continue with study participation, or may affect the study's scientific design, integrity, or its resultant data.

a. All MRDC personnel who discover or receive an allegation of human research noncompliance shall promptly report the potential noncompliance to their institution's HPD or designee. The HPD will gather preliminary information about the allegation or discovery and, will notify the IRB Chair and the Institutional Official (IO), if warranted.. The HPD, in consultation with the IRB Chair or IO, may require further investigation of the incident. For discoveries or allegations of noncompliance involving the USAMRDC subordinate commands reported to or discovered by OHARO, the OHARO shall refer the matter to the appropriate IO and HPD for investigation when discoveries or allegations are at the individual or protocol level; when discoveries or allegations of institutional noncompliance related to USAMRDC subordinate commands arise, MRDC OHARO may coordinate or conduct the investigation and review.

b. Discoveries or allegations of potential noncompliance in the conduct of research may come from a variety of sources, such as the investigator or study team, the study monitor, Human Research Protection Program (HRPP) personnel, IRB members, research participants or their friends or family, institutional personnel, the media, or anonymous sources. Discoveries or allegations of noncompliance must be promptly documented, investigated, adjudicated, and reported as required herein. Initial discoveries or allegations must be documented in as much detail as possible; this documentation will serve as the basis for subsequent investigation to validate or refute the allegation or suspicion.

c. Based on the gravity or magnitude of an unsubstantiated discovery or allegation (e.g., possible public disclosure of an event, subject injury), the subordinate command may send an initial notification of potential serious or continuing noncompliance to the Commanding General, MRDC, and the Director, OHARO before the investigation and review is initiated or completed.

d. Based on the nature and substance of the situation and/or expertise required during the investigation, the IO may delegate the investigation to an experienced IRB member or staff person, a subcommittee, or other qualified individual(s). Consultants or OHARO staff may also be involved in an investigation as appropriate. The IO may refer investigation of possible noncompliance to the MRDC OHARO if the situation involves, or could involve, institutional noncompliance by a MRDC subordinate laboratory, if there is potential conflict of interest among the IRB members, IO, or HPD, or if the allegation cannot be investigated adequately at the local

level. Potential noncompliance that may also involve “research misconduct” (i.e. plagiarism, falsification or fabrication of data) must be investigated in accordance with DoDI 3210.7, Research Integrity and Misconduct and MRDC Policy “Research Integrity and Misconduct.”

e. If the investigation substantiates the noncompliance or if other instances of noncompliance are identified, the investigation results must be reported to the HPD, IO, and the IRB Chair. The IRB must review all incidents of substantiated noncompliance.

f. All investigation activities must be fully documented. The report will contain, at a minimum, a detailed description of the allegations, investigation findings, corrective actions taken to date, and recommendations for any further corrective action and prevention.

g. Unsubstantiated discoveries or allegations of noncompliance shall be reported to the HPD (and IRB Chair, and IO if they received a preliminary notification). The HPD or IRB Chair, in consultation with the IO, may require further investigation of the incident.

20-2. IRB review

a. The IRB must review noncompliance at a convened meeting. The investigator(s) or study personnel who are the subject of investigation must be allowed the opportunity to be present to address the IRB. The convened IRB must review the results of the investigation and:

(1) Determine whether the investigation was sufficient. The IRB may require additional investigation before making a determination regarding noncompliance if it finds that the investigation was insufficient. Alternatively, the IRB may refer the investigation to the next higher authority for further investigation (e.g. MRDC OHARO).

(2) Determine whether the noncompliance meets the definition of serious and/or continuing noncompliance as defined herein.

(3) Exercise its authority in accordance with 32 CFR 219 to take the following corrective actions, as appropriate, for research that is not being conducted in accordance with the IRB’s requirements or that has been associated with unexpected serious harm to subjects:

(a) Require modifications to the research.

(b) Require additions or modifications to the information provided to research subjects.

(c) Require continuing review more frequently than once annually.

(d) Temporarily stop new enrollment in a protocol, pending corrective actions.

(e) Suspend or terminate the protocol.

(4) Recommend to the IO additional corrective actions to address substantiated noncompliance.

(5) The IRB minutes must adequately reflect the discussion of issues presented in the noncompliance investigation and discussion and resolution of controverted issues; include the determination of the IRB for whether the noncompliance constitutes serious and/or continuing noncompliance; state related actions taken by the IRB (e.g. suspension or termination of the

protocol, or required modifications); and include any additional corrective actions recommended to the IO.

(6) Promptly notify the HPD and IO of the outcome of the meeting and the IRB's determinations, stipulations, and recommended corrective actions.

(7) Promptly provide investigators written notification of the IRB's determination along with a statement of the reasons for its decision and stipulated actions. Investigators must respond to the requirements of the IRB in writing.

20-3. Determining Noncompliance

a. If the investigation substantiates the allegation of noncompliance, or if other instances of noncompliance are identified, the investigation results will be reported to the convened HQ MRDC 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 noncompliance, serious noncompliance, and/or continuing noncompliance.

b. Only the convened HQ MRDC IRB can make a determination of noncompliance. The convened IRB will review the results of the investigation and recommendations. The IRB will:

(1) Determine whether the investigation was sufficient. The IRB may require additional investigation before making a determination regarding noncompliance if it finds that the investigation was insufficient. Alternatively, the IRB may refer the investigation to the next higher authority for further investigation (e.g., MRDC OHARO).

(2) Determine whether noncompliance has occurred and, if so, whether the noncompliance meets the definition of serious and/or continuing noncompliance.

(a) Noncompliance: Failure of a person, group, or organization to act in accordance with a law, regulation, or policy governing human subjects research, the requirements and/or determinations of the overseeing IRB, or the research protocol.

(b) Serious noncompliance: Failure of a person, group, or institution to act in accordance with federal and DoD laws, regulations, or policies governing human subjects research, or with determinations or requirements of the IRB such that the failure could adversely affect the rights, safety, or welfare of a human subject; place a human subject at increased risk of harm; cause harm to a human subject; affect a human subject's willingness to participate in research; or damage or compromise the scientific integrity of research data.

(c) Continuing noncompliance: A pattern of actions or omissions suggesting a likelihood that, without intervention, instances of non-compliance will recur. A repeated unwillingness to comply with, or a lack of knowledge of, federal and DOD laws, regulations, or policies governing human subjects research, or with determinations or requirements of the IRB. Instances of continuing noncompliance may or may not constitute serious noncompliance.

(3) Exercise its authority in accordance with 32 CFR 219 to take the following corrective actions, as appropriate, for research that is not being conducted in accordance with the IRB's requirements or that has been associated with unexpected serious harm to subjects:

(a) Require modifications to the research.

(b) Require additions or modifications to the information provided to research subjects.

(c) Require continuing review more frequently than once annually.

(d) Temporarily stop new enrollment in a protocol, pending corrective actions.

(e) Suspend or terminate the protocol.

(4) Recommend to the IO additional corrective actions to address substantiated noncompliance. Such recommended actions may include, but are not limited to:

(a) Requiring investigator and/or staff undergo training in specific areas relevant to the type of noncompliance.

(b) Requiring investigator supervision by a qualified mentor.

(c) Requiring addition of qualified study team members.

(d) Requiring the study team to perform periodic self-assessments of study procedures and/or record management.

(e) Requiring notification to subjects of noncompliance (e.g., data breach).

(f) Re-consenting subjects with updated or corrected consent forms.

(g) Mandating additional safeguards such as third-party monitoring or auditing of research/consent process/recruiting.

(h) Limiting or prohibiting further use of data and/or specimens collected.

(i) Limiting or prohibiting publication of study results.

(j) Prohibiting individual investigators from participation in the research protocol.

(k) Notifying research partners, funders, and/or collaborators of the findings of noncompliance and/or required corrective actions, if applicable.

20-4. Reporting Requirements

a. 32 CFR 219.108(a)(4) and 21 CFR 56.108(b)(2) require “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. IOs must promptly report determinations of serious or continuing noncompliance to the OHARO and Senior Designated Official in accordance with MRDC Policy “Event Reporting Requirements for Human Subjects Research Conducted by the USAMRDC.” The OHARO will then report to DoD Office of Human Research Protections (DOHRP).

c. Documents submitted must include an executive summary and a detailed report containing the following information:

(1) Study information, including name of the institution conducting the research and site of the noncompliance; title of the research project in which the noncompliance occurred; name of the principal investigator; and log number(s) of the research project assigned by the IRB and the proposal or award number of any applicable federal award(s) (e.g., grant, contract, or cooperative agreement).

(2) A brief summary of the study (e.g., purpose and design).

(3) A detailed description of the event(s) determined to constitute noncompliance, including assessment of impact on the safety, rights, and welfare of human subjects.

(4) The IRB's determination that the noncompliance is serious and/or continuing and stipulated actions, and additional corrective actions required by the 10.

(5) Current status of remediation and follow-up of subjects impacted by the noncompliance.

d. Other federal agencies such as the Department of Health and Human Services, Office of Human Research Protections (OHRP) or the Food and Drug Administration (FDA) may require prompt reporting of findings of serious and/or continuing noncompliance. Reporting to these agencies will depend on the funding for the study found to be noncompliant and/or whether the study is subject to FDA regulations. The 10 must ensure reporting to these agencies in accordance with OHRP and FDA regulations.

e. Noncompliance determinations that are neither serious nor continuing do not require reporting outside the institution.

20-5. Appeal Process

a. Investigators may appeal the HQ MRDC IRB’s findings of noncompliance, in writing, documenting the reasons for the appeal (within 30 days of being notified of the IRB’s decision).

b. Investigators shall provide the written appeal along with any supporting documents through their Institutional Official to the HQ MRDC 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 MRDC IRB, and the investigator will be invited to attend the meeting to address issues surrounding the appeal. Written notification of the HQ MRDC IRB’s decision regarding the appeal will be sent to the investigator and his/her Institutional Official following the meeting.

c. The investigator is bound by the IRB’s decision prior to and during an appeal.

d. Further Appeal. If, following appeal to the HQ MRDC IRB, an investigator disputes the appeal outcome, the investigator may further appeal to his/her Institutional Official. The Institutional Official may deny the appeal, or consult with OHARO to identify a process to address the specific concerns of the investigator.

e. Neither the Institutional Official nor any HQ MRDC official or committee may overturn the HQ MRDC IRB findings of noncompliance, nor exert undue pressure on the HQ MRDC IRB to reverse a decision.

Chapter 21. Suspension or Termination of IRB Approval

a. The HQ MRDC IRB has the authority to suspend or terminate approval of research under it purview when it determines that the research has not been conducted in accordance with the IRB's requirements, the research has been associated with unexpected serious harm to subjects, or there is evidence of serious or continuing noncompliance with federal regulations. Any suspension or termination of approval shall include a statement of the reasons for the IRB's action (32 CFR 219/21 CFR 56.113).

b. Considerations for the HQ MRDC IRB suspending or terminating research include but are not limited to:

(1) Additional actions needed to protect the rights and welfare of currently enrolled subjects;

(2) Whether procedures for subject withdrawal take into account their rights and welfare (e.g., making arrangements for medical care outside of a research study, transfer to another researcher, and continuation in the research under independent monitoring);

(3) The need to inform current subjects of the suspension or termination.

c. Suspension or termination of the HQ MRDC IRB's approval of a study shall be promptly reported to the Principal Investigator, his/her Institutional Official, OHARO. OHARO will then report the suspension or termination to ASD,R&E and the funding program, if applicable. 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) shall also be notified. The HQ MRDC IRB Director or Deputy Director will ensure coordination of prompt reporting to all required entities, to include the Director, OHARO and CG, MRDC as required by Command Policy "Event Reporting Requirements for Human Subjects Research Conducted by the USAMRDC".

d. IRB approval suspension or termination may occur at any time during the period for which IRB approval had been granted. Notification of the suspension or termination, including a statement of the reasons for the suspension or termination, will be promptly reported to the investigator, appropriate institutional officials, and the appropriate federal agency supporting the research (if applicable). The investigator will be given an opportunity to respond to the IRB in person or in writing. The IRB will establish procedures to ensure that the rights and welfare of currently enrolled subjects are protected, and subjects are not placed at risk and receive appropriate care.

Chapter 22. Reporting the HQ MRDC IRB's Findings and Actions

32 CFR 219.108(4)(i) requires written procedures that the IRB will follow for reporting its findings and actions to the investigator and the institution.

22-1. Notification of Actions Based on the HQ MRDC IRB's Stipulations, Requirements, and Recommendations

The final determination made by the HQ MRDC 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 MRDC IRB's determination with accompanying stipulations and recommendations. If stipulations require submission of revisions to the protocol and/or consent document, such revisions should be submitted to the OHARO IRB Office as soon as possible.

22-2. Notifications Regarding UPIRTSOs in a Study

Any findings by the HQ MRDC IRB based on the review of UPIRTSOs (See Chapter 18) in a study shall be promptly reported to the Principal Investigator of the research protocol, and his/her Institutional Official. In HHS- sponsored or FDA regulated research, the appropriate institutional officials and the appropriate department or agency head (i.e. OHRP or FDA) shall be similarly notified promptly of any UPIRTSOs. The HQ MRDC IRB Director or Deputy Director will ensure coordination of prompt reporting to these required entities.

22-3. Notification Regarding Noncompliance With Requirements

Regarding matters of substantiated findings of noncompliance with the regulatory requirements of DoD or its components, MRDC's formal notification of the Principal Investigator and his/her Institutional Official, the CG, MRDC, and the OHARO shall be accomplished by the OHARO 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 20 of this document.) The HQ MRDC IRB Director or Deputy Director will ensure coordination of prompt reporting to all required entities, to include the Director, OHARO and CG, MRDC.

Chapter 23. HQ MRDC IRB Records

This chapter describes how the HQ MRDC IRB prepares and maintains adequate documentation of IRB activities in accordance with 32 CFR 219.115/21 CFR 56.115 and other applicable regulations. The HQ MRDC IRB uses electronic IRB systems, local intranet systems, and hardcopy paper files for documentation of IRB activities.

23-1. IRB Protocol Master Files

Files are prepared and maintained for all human subjects protocols reviewed by the HQ MRDC IRB. All submissions are assigned a unique log number for use in tracking.

IRB master files include the following documents as appropriate/applicable:

r. 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 MRDC IRB official letters/memos (e.g., IRB official meeting outcome letter, IRB approval memo, waivers of HIPAA authorization).

e. Protocol reviews (e.g., OHARO IRB Office pre-review and IRB member reviewer checklists, Memoranda for the Record (MFRs), response to stipulations, DSMB or DMC reports, consultant reports), and HIPAA Authorization waiver/alteration review documentation.

f. Additional local IRB documentation (e.g., for OCONUS protocols).

g. Protocol (initial submission and all subsequent approved versions).

h. Consent document (and HIPAA Authorization as applicable) (initial submission and all subsequent approved versions).

r. Study instruments (e.g., questionnaires, recruitment material).

j. Scientific review documentation.

k. HQ MRDC IRB read-ahead packets (includes items related to full IRB review of a protocol).

l. CVs/biographical sketches, human subjects protection training documentation, COI statements for Principal Investigator and all other study personnel listed on the protocol, as applicable.

m. Investigator’s Brochure/device manual/product information/insert, FDA forms and communications.

n. DSMB/DMC documents (e.g. charter, membership information).

o. Consultations (SME, JAG, ORA) to include correspondence, consultation report/memo, references, etc.

p. Documentation related to continuing review, to include documentation of the rationale for requiring continuing review of research that otherwise would not require continuing review.

q. Amendments and supporting documents.

r. Reportable events (e.g., adverse event reports, research monitor reports, deviations reports, etc.).

s. Any statements of significant new findings to be provided to subjects.

t. Post-approval compliance monitoring (PACM report, checklists, etc.).

u. Protocol closure documents (final study reports, IRB review documents).

v. Award documents.

w. Other related documents (Sponsor letters, proof of clinical trial insurance, etc.).

23-2. 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 as per 32 CFR 219.102, or determined to be exempt under one or more categories at 32 CFR 219.104, including documentation of the rationale or basis for the finding and the applicable exemption category(ies).

23-3. 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 showing each member's area of contribution to IRB deliberations, and any employment or other relationship between each member and DoD is maintained by the IRB Office leadership. Whenever the membership of the IRB changes, a new dated roster is produced.

23-4. Minutes of HQ MRDC IRB Meetings

The minutes of HQ MRDC 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, continuing review, or other life cycle action by the convened IRB. Reasons for votes of disapproval will be documented. 32 CFR 219.115 and 21 CFR 56.115 requires that the minutes of IRB meetings shall be recorded in sufficient detail to show:

a. Attendance at the meetings. The minutes will record the names and earned degrees of the participating IRB members. The membership roster included as an enclosure to all minutes will reflect category of membership (i.e., primary or alternate member, affiliated or non-affiliated member, scientist or non-scientist member).

b. Actions taken by the HQ MRDC 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 document the findings where the regulations require specific findings on the part of IRB, such as:

a. Approving research with waiver or alteration of informed consent.

b. Approving research with waiver of the documentation of informed consent.

c. Approving research involving pregnant women or children.

d. Approving research with waiver or alteration of HIPAA authorization.

e. Determining that the proposed use of an investigational device satisfies the FDA criteria for non-significant risk device research or that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.

The minutes will also include the names of all non-member persons attending any part of the IRB meeting (e.g., IRB staff, consultants, guests).

23-5. Other HQ MRDC IRB Correspondence

Other correspondence to or from the HQ MRDC IRB is retained. Examples of such correspondence include but are not limited to findings or recommendations on general issues to CG, MRDC; official communications with FDA, and other regulatory bodies; lists of protocols and protocol actions reviewed and approved by expedited review; and post-approval compliance monitoring documentation and responses from the research site regarding any findings.

23-6. Security of Records

a. All HQ MRDC IRB records will be kept securely in buildings requiring access badges, in locked storage rooms, locked filing cabinets, on computers requiring Common Access Card access, 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 MRDC IRB minutes under applicable Freedom of Information Act laws. If rights of access are at all unclear, the Director, OHARO, will consult with the SJA of MRDC.

23-7. Records Retention

HQ MRDC IRB records will be retained as required by DoDI 3216.02, AR70-25, AR 25-400, and all other applicable requirements. The OHARO IRB Office will ensure retention of HQ MRDC IRB records:

a. For at least three years after completion of the research as required under 32 CFR 219/21 CFR 56.115.

b. For six years after the date of HIPAA-related documentation creation or the date when it last was in effect, whichever is later.

Chapter 24. Transfers of IRB Review

Research projects that were previously approved by one IRB may be transferred to another IRB for a variety of reasons. In order to assure continuous IRB oversight and protection of human subjects with minimal disruption of research activities, the transferring and receiving IRBs must work closely with the investigator throughout the transition process.

a. Institutions wishing to transfer IRB review of research protocols to or from the HQ MRDC IRB should first contact the OHARO IRB Office to discuss their request. All transfers must be justified.

(1) If an institution wishes to transfer IRB review for research protocols from another IRB to the HQ MRDC IRB, the institution must submit a request for transfer with a copy of the transferring IRB's review of the research protocol. The HQ MRDC IRB will acknowledge receipt of the request and, based upon the justification provided for the transfer, determine its feasibility and coordinate or decline the transfer.

(2) If an institution wishes to transfer IRB review from the HQ MRDC IRB to another IRB, the institution must submit a request for transfer to the OHARO IRB Office, which will acknowledge receipt of the request and coordinate the transfer.

b. When transferring or receiving IRB review, the HQ MRDC IRB will agree in writing (e.g., email communication, MFR, agreement) with the transferring or receiving IRB on the following considerations:

(1) The specific project(s) for which IRB oversight will be transferred.

(2) The effective date or for transfer of oversight.

(a) This may be a predetermined date or may be contingent upon the review and acceptance of the research project by the receiving IRB.

(b) If the receiving IRB decides to perform an initial review of the research project, then it will notify the transferring IRB of the date of its approval and acceptance of oversight responsibilities.

(3) Assuring retention of IRB records.

(a) Prior to accepting oversight of a project, the receiving IRB will obtain copies of relevant records (e.g., protocol, proposal, consent document, minutes of IRB meetings at which the research was reviewed, etc.).

(b) The OHARO IRB Office and the transferring/receiving institution will complete a document inventory and provide written verification.

(4) The type of review the receiving IRB will perform before accepting responsibility for each project.

(a) There is no regulatory requirement for the receiving IRB to review the project prior to the next continuing review date established by the original IRB.

(b) The receiving IRB may choose to conduct an initial review or a continuing review prior to accepting oversight responsibility or the IRB Chair or designee may perform an informal assessment of the research project.

(5) The due date for the next continuing review. If the receiving IRB performs an initial or continuing review at the time of research project transfer, it may to choose to maintain the anniversary date established by the original IRB or to establish a new date of approval.

(6) Whether the consent document needs to be revised (e.g., to provide new contact information for subjects) or previously enrolled subjects notified of the new IRB.

(7) Which key parties require notification of the IRB transfer (e.g., Principal Investigator, Data Safety Monitoring Board, sponsor, etc.).

Chapter 25. 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 noncompliance are among the specific objectives of the OHARO IRB Office's QA activities. The QA activities include:

a. Education and Training. All HQ MRDC IRB members and OHARO IRB Office HSPSs receive training on the Belmont Principles, the Nuremburg Code, 32 CFR 219, DoD and Army human subjects protection regulations, and the IRB's policies and procedures. Board members and OHARO IRB Office staff are provided with electronic and hard copy regulatory reference materials to assist them in their reviews of protocols. If funds are available, Board members and OHARO IRB Office staff may be funded to attend the Public Responsibility in Medicine and Research National IRB Conference. Information to IRB members and staff on current topics in human subjects protection is forwarded on an ongoing basis, and continuing education materials are shared with IRB members along with meeting materials.

b. Encouraging and soliciting feedback to and from the HQ MRDC IRB Chair, Vice Chair, members, and OHARO IRB Office staff regarding their qualifications and performance, e.g., post-IRB meeting "hot wash" discussions for challenging agenda items, surveys of IRB members regarding their opinions of IRB operations, annual performance reviews and appraisals for staff members.

c. 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 OHARO IRB Office staff members or the HQ MRDC IRB Chair/Vice Chair. The Director and Deputy Director, IRB Office discuss common issues and any recurring errors with IRB Office HSPS during staff and process improvement working group meetings to help ensure review product consistency among the staff.

d. HQ MRDC IRB members conduct expedited and convened Board reviews using standardized regulatory checklists to ensure that all criteria for approval are satisfied.

e. 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.

f. The Director and Deputy Director, IRB Office, and IRB Chair review the HQ MRDC IRB policies and procedures at least biennially to ensure relevancy and consistency, and to address evolving needs of the IRB's customers. The OHARO IRB Office staff conduct regular working group meetings to address updates to existing materials and to develop new materials. The OHARO IRB Office provides training sessions for IRB members and customers following significant revisions to policies and procedures, and solicits input and feedback on new templates, tools, and guidance documents.

g. The Director and Deputy Director, IRB Office will conduct biennial "voice of the customer" surveys of investigators and IRB members to determine level of satisfaction with the HQ MRDC IRB and IRB Office and solicit suggestions for improvement.

h. The Director and Deputy Director, IRB Office will conduct periodic review and reporting to the Director, OHARO, of HQ MRDC IRB protocol review and approval metrics to include, e.g., times to approval, challenges to achieving timely approvals, unique review problems, reasons for

protocol expirations. The goal is to use customized reports generated on a monthly basis from the OHARO IRB Office Electronic Grants System (EGS) tracking database (e.g., approval status, continuing review expiration date, times to approval), to provide the Director and Deputy Director, IRB Office with ongoing visibility of IRB operations.

i. Selection of one or more protocols per month or per quarter for internal audit by OHARO IRB Office staff, depending upon the available resources.

j. The DoD Office for Human Research Protections (DOHRP) also conducts assessments of the HQ MRDC IRB as part of their oversight of the DoD Component Human Research Protection programs.

Chapter 26. Component-level Review and Oversight of HQ MRDC IRB Actions

DoDI 3216.02 requires Component-level administrative review (CLAR) and approval of specific categories of non-exempt human subjects research. When the HQ MRDC IRB approves research in the following categories, the Director or Deputy Director, OHARO IRB Office will ensure that the required CLAR and approval takes place. CLAR review and approval will be conducted by the Director, OHARO or another individual who has been delegated CLAR approval authority.

a. Research conducted in a foreign country unless the research will be conducted by an established DOD overseas research institution and the research will be conducted in the host country, or the research will include only DOD personnel who are U.S. citizens as human subjects.

b. Research that requires a waiver of 10 USC 980 to permit conduct of the research under the exception from informed consent requirements.

c. Research involving a nonviable living human fetus ex utero or a living human fetus ex utero for whom viability has not been ascertained as covered under sections 289g-289g-2 of title 42, USC.

d. Research involving large-scale genomic data, such as that derived through whole-genome sequencing, from a target population of DOD-affiliated personnel as defined in DODI 3216.02. This provision does not include incidental participation of DOD-affiliated personnel in research that enrolls a broader population, and does not extend to research on targeted genes, genotypes, or phenotypes that are non-large-scale.

e. Research involving pregnant women, fetuses, or neonates that presents an opportunity to understand, prevent, or alleviate a serious problem affecting their health or welfare in accordance with part 207 of 45 CFR 46, Subpart B.

f. All research involving prisoners, to include research in which a previously enrolled subject becomes a prisoner in accordance with 45 CFR 46, Subpart C.

g. Research involving children that presents an opportunity to understand, prevent, or alleviate a serious problem affecting their health or welfare and provides no prospect of benefit to the individual participant in accordance with part 407 of 45 CFR 46, Subpart D and part 54 of 21 CFR 50, Subpart D.

h. Research that constitutes classified human subjects research as defined in DODI 3216.02. Appendix A. Ethical Principles, Federal Requirements, Guidelines

Appendix A. Ethical Principles, Federal Requirements, Guidelines

Ethical Principles

Nuremburg Code, 1946

Belmont Report, *Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, 18 April 1979: 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 MRDC IRB's written operational policies and procedures are based primarily on the requirement of these Federal regulations and also other requirements.

World Medical Association (WMA) Declaration of Helsinki: *Ethical Principles for Medical Research Involving Human Subjects*. *64th WMA General Assembly, Fortaleza, Brazil, October 2013*

Council for International Organizations of Medical Sciences - *International Ethical Guidelines for Health-Related Research Involving Humans* (Council for Organizations of Medical Sciences ((CIOMS)) International Ethical Guidelines) Prepared by CIOMS in collaboration with the World Health Organization (WHO), 2016

International Conference on Harmonization (*ICH) - Harmonized Tripartite Consolidated Guideline for Good Clinical Practice: Efficacy Guideline – 6(R2)* (ICH-GCP-E6(R2)), 2016

Laws, Regulations, Directives, and Instructions

The HQ MRDC IRB operates under the following statutory laws, Federal regulations, DoD Directives, DoD Instructions, Department of Army regulations.

Statutory Laws

10 USC 980 (last amended 2002), *Limitation on Use of Humans as Experimental Subjects*

10 USC 1107 (as released on 18 March 2004), *Notice of Use of an Investigational New Drug or a Drug Unapproved for its Applied Use* (see Chapter 16)

24 United States Code 30, *Payments to Donors of Blood for Persons Undergoing Treatment at Government Expense*, 1 June 2003

Federal Regulations

32 Code of Federal Regulations (CFR) 219, *Protection of Human Subjects*, effective 21 January 2019 (also called the Federal Policy or 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; Subpart D: *Additional Protections for Children involved as Subjects in Research; Subpart E: Registration of Institutional Review Boards*

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)

DoD Directives (DoDD) and Instructions (DoDI)

DoDI 3210.7, DoD *Research Integrity and Misconduct*, 14 May 2004: *Research Integrity and Misconduct*. This Instruction supplements the policy established by paragraph 4.8. of DoDI 3216.02 and implements subparagraph 5.1.5 of DoDI 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.

DoDI 3216.02, *Protection of Human Subjects and Adherence to Ethical Standards in DoD-Conducted and -Supported Research*, June 29, 2022: 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."

DoDD 5400.11-R, *DoD Privacy Program*, May 14, 2007

DoD Manual 6025.18, *Implementation of the Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule in DoD Health Care Programs*, March 13, 2019

DoDI 6025.18, *Health Insurance Portability and Accountability Act (HIPAA) Privacy Rule Compliance in DoD Health Care Programs, March 13, 2019*

DoDI 6200.02: DoD *Application of Food and Drug Administration (FDA) Rules to Department of Defense Force Health Protection Programs*, February 27, 2008: 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 MRDC IRB (formerly known as the Human Subjects Research Review Board or HSRRB) is designated as the single IRB 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.

Department of the Army (DA) Regulations

Army Regulation (AR) 70-25, *Use of Volunteers as Subjects of Research*, Jan 25, 1990: This regulation establishes Army policy for implementation of Federal regulations for the protection of human research subjects (32 CFR 219), and reflects Army policy for implementation of DoDI 3216.02 regarding the protection of human research subjects.

AR 40-7, *Use of US Food and Drug Administration-Regulated Investigational Products in Humans Including Schedule I Controlled Substances,* Oct 19, 2009: 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 US Drug Enforcement Administration Schedule I controlled substances in humans and animals where DA facilities, personnel, or financial support are used.

Other

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

Message, ALARACT 031/2008, *Army Human Subjects Protection Requirements* DTG 141557Z Feb 08

DDR&E Minimum Education Requirements for DoD Personnel Involved in Human Research Protection (MERF), August 16, 2012

Food and Drug Administration (FDA) guidance documents for good clinical practice (GCP) and the conduct of clinical trials

Appendix B. Definitions

Federal Definitions

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.

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.

Clinical Trial – A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of the interventions on biomedical or behavioral health-related outcomes.

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.

Federal department or agency - A federal department or agency (the department or agency itself rather than its bureaus, offices or divisions) that takes appropriate administrative action to make this policy applicable to the research involving human subjects it conducts, supports, or otherwise regulates (*e.g.,* the U.S. Department of Health and Human Services, the U.S. Department of Defense, or the Central Intelligence Agency).

Institution - Any public or private entity or agency (including federal, state, and other agencies).

Interaction - Communication or interpersonal contact between investigator and subject.

Intervention - Both physical procedures by which information or biospecimens are gathered (*e.g.,* venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.

Private information - Information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information that has been provided for specific purposes by an individual and that the individual can reasonably expect will not be made public (*e.g.,* a medical record).

Identifiable private information - Private information for which the identity of the subject is or may readily be ascertained by the investigator or associated with the information.

Identifiable biospecimen - A biospecimen for which the identity of the subject is or may readily be ascertained by the investigator or associated with the biospecimen.

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. If there is no

applicable law addressing this issue, *legally authorized representative* means an individual recognized by institutional policy as acceptable for providing consent in the nonresearch context on behalf of the 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 that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. For purposes of this part, the following activities are deemed **not to be research**:

(1) Scholarly and journalistic activities (*e.g.,* oral history, journalism, biography, literary criticism, legal research, and historical scholarship), including the collection and use of information, that focus directly on the specific individuals about whom the information is collected.

(2) Public health surveillance activities, including the collection and testing of information or biospecimens, conducted, supported, requested, ordered, required, or authorized by a public health authority. Such activities are limited to those necessary to allow a public health authority to identify, monitor, assess, or investigate potential public health signals, onsets of disease outbreaks, or conditions of public health importance (including trends, signals, risk factors, patterns in diseases, or increases in injuries from using consumer products). Such activities include those associated with providing timely situational awareness and priority setting during the course of an event or crisis that threatens public health (including natural or man-made disasters).

(3) Collection and analysis of information, biospecimens, or records by or for a criminal justice agency for activities authorized by law or court order solely for criminal justice or criminal investigative purposes.

(4) Authorized operational activities (as determined by each agency) in support of intelligence, homeland security, defense, or other national security missions.
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:(i) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens; or (ii) Obtains, uses, studies, analyzes, or generates identifiable private information or identifiable biospecimens. NOTE: The Food and Drug Administration (FDA) defines a *human subject* as an individual who is or becomes a subject 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.

Institution - Any public or private entity, or department or agency (including federal, state, and other agencies).

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.

Public Health Authority – An agency or authority of the United States, a state, a territory, a political subdivision of a state or territory, an Indian tribe, or a foreign government, or a person or entity acting under a grant of authority from or contract with such public agency, including the employees or agents of such public agency or its contractors or persons or entities to whom it has granted authority, that is responsible for public health matters as part of its official mandate.

Written or in writing – A reference to writing on a tangible medium (e.g. paper) or in an electronic format.

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 LAR. 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 MRDC 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 LAR. 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.

Collaborating Institution: An institution engaged in human subjects research through the involvement of its investigators in at least one aspect of a study, including protocol development, subject recruitment ,screening or consent processes, performance of research interventions, interactions, conducting data analysis, and/or presentation/publication of results. Collaborating institutions also may be institutional performance sites.

Collaborative Research: Research protocols executed by investigators from at least two different institutions with generally equivalent, but perhaps different, contributions to the conduct of the research. Can range from simple to complex:

a. Simple: research conducted at one institution with involvement from one or more institution's investigators.

b. Complex: multi-site research developed by a lead institution or sponsor, perhaps in collaboration with others, that takes place at two or more performance sites.

Cooperative Research: Research projects that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy. Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research. The following is not subject to this provision: 1) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or 2) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

Continuing noncompliance - A pattern of actions or omissions that suggest a likelihood that, without intervention, instances of noncompliance 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 subjects.

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.

Institutional Performance Site: Individuals and institutions engaged in conducting research protocols including recruiting or screening, obtaining consent, conducting interventions and interactions, and reporting to the lead institution.

Key Research Personnel - Persons listed on human research protocols who have direct contact with subjects or have contact with subjects' identifiable data, records, or biological samples (e.g. tissue, blood, urine, plasma, saliva).

Lead Institution: The institution in charge of the core research protocol or sponsor protocol, that manages, coordinates, and directs the institutional performances sites.

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.

Noncompliance - Failure of a person, group, or organization to act in accordance with a law, regulation, or policy governing human subjects research, the requirements and/or determinations of the overseeing IRB, or the research protocol.

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 OHARO IRB Office for review.

Serious noncompliance - An action or omission that adversely affects the rights, safety, or welfare of subjects, placing subjects at increased risk of harm, or causing harm to subjects.

Short Form Consent - A written informed consent document that summarizes the required elements of informed consent to be presented orally to the subject or his or her LAR.

Single IRB: A single IRB is an IRB that reviews, approves, and oversees certain research protocols on behalf of institutions that may or may not have their own IRB(s).

Secondary research use: The re-using for research purposes of identifiable and non-identifiable information and biospecimens that are collected for some other primary or initial activity (such as from research studies other than the proposed research study).

Glossary of Abbreviations

Abbreviation	Meaning
AE	Adverse Event
AMEDD	Army Medical Department
AR	Army Regulation
AS	Administrative Simplification
ASG/DCS-QS	Assistant Surgeon General/Deputy Chief of Staff for Quality and Safety
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	US 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
HPD	Human Protections Director
HQ	Headquarters
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
OHARO	Office of Human and Animal Research Oversight
OHRO	Office of Human Research Oversight
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
USAMRDC	United States Army Medical Research and Development Command
USC	United States Code
USCENTCOM	United States Central Command
VA	Veterans Affairs
VRMS	Volunteer Registry Management System
WHO	World Health Organization