Clinical Investigation Regulatory Office

OPERATIONAL POLICIES AND PROCEDURES

US Army Medical Department Center & School
Bldg 2268, 1608 Stanley Road
Fort Sam Houston, Texas 78234-5055
Telephone: (210) 221-2511; DSN 471-2511
Fax: (210) 295-0244

Version 10/12/06

Table of Contents

Glossary of Abbreviations

Abbreviation	Meaning
AMEDD	Army Medical Department
AE	Adverse Event
APR	Annual Progress Report
AR	Army Regulation
CFR	Code of Federal Regulation
CI	Clinical Investigation
CIP	Clinical Investigation Program
CIRO	Clinical Investigation Regulatory Office
COI	Conflict of Interest
CRADA	Cooperative Research and Development Agreement
CV	Curriculum Vitae
DA	Department of the Army
DDR&E	Department of Defense Research and Engineering
DHHS	Department Health and Human Services
DoD	Department of Defense
DoDD	Department of Defense Directive
DoDI	Department of Defense Instruction
FDA	Food and Drug Administration
FHP	Federal Health Protection
FOI	Freedom of Information
FR	Federal Register
FWA	Federal Wide Assurance
GTMR	Greater than Minimal Risk
HHS	Department of Health and Human Services
HRPO	Human Research Protections Office
HSP	Human Subjects Protection
HSPD	Human Subjects Protection Division
HSRRB	Human Subjects Research Review Board
HUC	Human Use Committee
ICH-GCP-E6	International Conference on Harmonization – Good Clinical Practice – Efficacy Guideline 6
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
JAG	Judge Advocate to the General
JCAHO	Joint Commission on Accreditation of Healthcare Organizations
MACOM	Major Army Command
MFR	Memorandum for Record
MTF	Medical Treatment Facility
OHRP	Office for Human Research Protections
OTSG	Office of the Surgeon General
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
QI	Quality Improvement

RDT&E	Research, Development, Test & Evaluation
SAE	Serious Adverse Event
SAV	Staff Assistance Visit
SJA	Staff Judge Advocate
TSG	The Surgeon General
USAMRMC	United States Army Medical Research and Materiel Command
USC	United States Code

Chapter I: Introduction - Protecting Human Research Participants

Medical research and materiel are critical to maintaining trained and ready Armed Services capable of rapid deployment and decisive victory. No one knows precisely what threats the United States will face in the future, but history suggests that victory will depend heavily on the presence of a superior medical technology base that can respond rapidly with required counter measures to emerging health threats. Military readiness requires research to develop and test innovative procedures, products and technologies. Much of this research involves the participation of human volunteers.

The Department of Defense (DoD) is committed to the protection of human research subjects and adherence to ethical standards in the conduct of DoD-supported research. The history of biomedical and behavioral research with human beings is filled with incidents in which research goals took precedence over the rights and welfare of the research subjects. Fortunately, over the past nearly six decades, the efforts of various domestic and international groups and ultimately the acts of the U.S. Congress have provided both the guiding principles as well as the regulatory framework for the protection of human beings who participate in research (see list of references to ethical principles and Federal requirements below).

In the late 1970s, substantial increases in the number of clinical research projects necessitated realigning responsibility for clinical investigations from the Human Use Review Office (HURO) of the Medical Research and Development Command (MRDC) to the Clinical Investigation Program Division (CIPD) of the Health Care Studies and Clinical Investigation Activity, a field operating agency of Health Services Command. Funding sources (P6 vs. P8) and research subject type (healthy volunteers vs. sick patients) formed the basis for delineating research programs between MRDC and CIPD.

During the redesign that led to the creation of the Army Medical Command (MEDCOM) in 1993, CIPD was renamed the Clinical Investigation Regulatory Office (CIRO) and moved to the AMEDD Center & School (AMEDDC&S). Although CIRO supervises clinical research at Army hospitals for the Commander of MEDCOM, the office was located within the AMEDDC&S because of limits on personnel authorizations within MEDCOM headquarters (HQ).

The location of CIRO within the AMEDDC&S is consistent with its primary focus of support for graduate medical and dental education, and other professional training programs. Army hospitals have an excellent track record of responsiveness and compliance with the decisions and guidance rendered by CIRO under its current level of authority.

CIRO's mission is to assure compliance with federal regulations for protection of human medical research subjects and for responsible use of animals in medical research and training. The Army clinical investigation program (CIP) improves health care and facilitates graduate medical education, graduate dental education, and other professional health education by stimulation of scholarly endeavor, retention of faculty, and introduction of new technology.

This document describes the CIRO's written policies and procedures and establishes the operational guidelines for effective oversight of the Army CIP with the regulatory requirements of DoD and Federal Law.

I. A. References to Ethical Principles and Federal Requirements

Nuremberg Code, 1946

Belmont Report, 1979

World Medical Association (WMA) Declaration of Helsinki: *Ethical Principles for Medical Research Involving Human Subjects*. 52nd WMA General Assembly, Edinburgh, Scotland, October 2000

International Conference on Harmonization (*ICH) - Harmonized Tripartite Consolidated Guideline for Good Clinical Practice: Efficacy Guideline - 6* (ICH-GCP-E6), 1 May 2001

10 United States Code (USC) 980, *Limitation on Use of Humans as Experimental Subjects*

10 United States Code 1107, *Notice of use of an investigational new drug or a drug unapproved for its applied use*, 2 January 2001

24 United States Code 30, *Payments to Donors of Blood for Persons Undergoing Treatment at Government Expense*, 1 June 2003

32 Code of Federal Regulations (CFR) 219, *Protection of Human Subjects*, 1 July 2004

21 CFR 50, *Protection of Human Subjects*, 1 April 2004

21 CFR 54 *Financial Disclosure by Clinical Investigators*, 1 April 2004

21 CFR 56, *Institutional Review Boards*, 1 April 2004

21 CFR 312, *Investigational New Drug (IND) Application*, 1 April 2004

21 CFR 812, *Investigational Device Exemptions (IDEs)*, 1 April 2004

Department of Defense Directive (DoDD) 3216.2, *Protection of Human Subjects and Adherence to Ethical Standards in DoD- Supported Research*, 25 March 2002

Department of Defense Instruction 3210.7, *Research Integrity and Misconduct*, May 14, 2004

DoDD 6200.2, *Use of Investigational new Drugs for Force Health Protection*, 1 August 2000
Office of the Secretary of Defense Memorandum, *Department of Defense (DoD) Guidance for Assurance of Compliance with the Federal Policy for the Protection of Human Subjects*, 10 June 1993

Army Regulation (AR) 40-7, *Use of Investigational Drugs and Devices and the Use of Schedule I Controlled Drug Substances*, 4 January 1991

AR 70-25, *Use of Volunteers as Subjects of Research*, 25 January 1990

AR 70-57; *Military–Civilian Technology Transfer;* 26 February 2004

AR 40-38, *Clinical Investigation Program*, 1 September 1989

AR 40-33; *The Care and Use of Laboratory Animals in DOD Programs, 16* February 2005

OTSG Regulation 15-2, *Human Subjects Research Review Board (HSRRB)*, 11 January 1989

OTSG Regulation 15-82, *HSRRB Subcommittee for Review of Materiel Test Plans and Protocols*, 1 May 1990

USAMRDC Reg 70-25 (20 April 1990)

USAMRMC Reg 70-25 (USAMRDC Reg 70-25 - as amended - July 2003)

MEDCOM Policy on Use of Animals for Medical Purposes (6 February 1994)

The List of Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) through an Expedited Review Procedure; 63 Federal Register (FR) 60364 – 60367; 9 November 1998

Food and Drug Administration (FDA) Information Sheets: Guidance for Institutional Review Boards and Clinical Investigators 1998, FDA

Office for Human Research Protections (OHRP) Compliance Activities: Common Findings and Guidance 30 November 2001, OHRP

I. B. Definitions

I. B. 1. Federal Definitions

The definitions, utilized in the Federal human subjects protections regulations at 32 CFR 219.102, are quoted below:

Department or Agency head - the head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated.

Institution - any public or private entity or Agency (including Federal, State, and other agencies).

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

Research - a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities which meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program which is considered research for other purposes. For example, some demonstration and service programs may include research activities. [Note that AR 70-25 states that the term *Research* does not include individual or group training of military personnel such as combat readiness, effectiveness, proficiency, or fitness exercises]

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 Food and Drug Administration). It does not include research activities which are incidentally regulated by a Federal Department or Agency solely as part of the Department's or Agency's broader responsibility to regulate certain types of activities whether research or non-research in nature (for example, Wage and Hour requirements administered by the Department of Labor).

Human subject - a living individual about whom an investigator (whether professional or student) conducting research obtains data through intervention or interaction with the individual, or identifiable private information. Intervention includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. *Interaction* includes communication or interpersonal contact between investigator and subject. *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

IRB - an Institutional Review Board established in accord with and for the purposes expressed in this policy.

IRB approval - the determination of the IRB that the research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

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

Certification - the official notification by the institution to the supporting Department or Agency, in accordance with the requirements of this policy, that a research project or activity involving human subjects has been reviewed and approved by an IRB in accordance with an approved assurance.

I. B. 2. Adverse Event Definitions

Specific Definitions taken from the Regulations for the Food and Drug Administration (FDA) and from the Guidance for the Industry by the International Conference on Harmonization (ICH):

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))

I. B. 3. CIRO's Working Definitions

Clinical Investigation - An organized inquiry in to clinical health problems for all conditions that are of concern in providing health care to the beneficiaries of the military healthcare system including active duty personnel, dependents, and retired personnel.

Intramural research - Research that is conducted within AMEDD Medical Treatment Facilities (MTF).

Extramural research - AMEDD-sponsored research that is conducted at non-AMEDD sites by non-AMEDD investigators.

Local IRB Review - Review conducted by the IRB of the institution where the research will be implemented.

IRB of Record - IRB that assumes primary responsibility for review and oversight of a protocol.
HSRRB - as the (First Level) IRB of "Record" – The HSRRB serves as the first-level IRB of record responsible for review and oversight of protocols. The HSRRB is the designated IRB of record for all DoD Contingency IND Protocols for Force Health Protection (DoDD 6200.2) and may serve as the IRB of Record for Army Commands that do not have their own Human Use Committees (AR 70-25(2-5.f)).

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 (DoDD 3216.2) ***This is not research.***

Test - A process by which data are accumulated to serve as a basis for assessing the degree to which an item or system meets, exceeds or fails to meet the technical or operational properties required (AR- 40-38).

Quality Control (QC) - Refers to activity that can be related to results of process, activity or product meeting written specifications or standards. QC focuses on identifying any shortcomings in the product and having them corrected before the product is complete. Identifying problems or shortcomings when they occur is the most important aspect of QC activities. In the case of a clinical trial, QC refers to the operational techniques and activities undertaken within the Quality Assurance system to verify that the requirements for quality of the trial related activities have been fulfilled.

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.

Quality Improvement (QI): Refers to every component, including personnel, of the institution that produces a particular product or performs a given activity, meeting the highest possible (the "ceiling") standards. QI is a proactive effort with a goal to continually improve processes as needed, based on root cause analyses of underlying problems.

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

Protocol Termination: A study is defined as "terminated" if it is closed involuntarily by the PI or the IRB: (i) due to protection issues, such as the occurrence of an adverse event that raises new safety concerns about the study; (ii) due to non-compliance issues regarding activity conducted by the research team that may be detrimental to the institution and / or the accrued subjects; (iii) if the PI 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; (iv) because of subject recruitment problems; and/or (v) when early data analysis leads to determination that further research would be fruitless.

Protocol Closed to New Patient Accrual: A study is defined as “closed to new patient accrual” (CTNPA) if the study (i) open for treatment and follow-up on currently enrolled patients, (ii) open for follow-up purposes only.

Protocol Completion: A study is defined as "completed" if it is closed voluntarily by the PI because: (i) the research team has completed all of the specific aims including data collection and analyses as identified in the research protocol; and (ii) the Pi has submitted the final report(s).

I. C. Clinical Investigation Regulatory Office

I. C. 1. CIRO’s Human Subject Protection Oversight Responsibilities

This includes the following activities:

a. Interpreting and updating Department of Army, Human Subjects Protection Regulations.

b. Providing interpretation of the applicable Federal, DoD and Army regulations.

c. Updating the CIRO's Policies regarding protections for human research participants.

d. Prepares Assurance of Compliance documents from the Army Medical Department Regional Medical Commands and submits to the ASG, FP for approval.

e. Maintain a clinical investigation research service (CIRS) database capturing all pertinent information on protocols received and CRADAs entered into by CIRO.

f. CIRO is the approving authority for investigational drug studies. Investigational drug studies submitted to CIRO will be reviewed within ten working days of receipt. The outcome of CIRO review will either be approval, disapproval, or request for revision. Properly revised studies will be expeditiously approved (ten working days or less) after receipt. (AR 40-38, 2-7d(1))

g. CIRO is the approving authority for investigational device studies. Investigational device studies submitted to CIRO will be reviewed within ten working days of receipt. The outcome of CIRO review will either be approval, disapproval, or request for revision. Properly revised studies will be expeditiously approved (ten working days or less) after receipt. (AR 40-38, 2-7d(2))

h. CIRO is the approving authority for emergency use of investigational drugs. Emergency use request required information is specified in the regulation. Requests for approval may be submitted by contacting CIRO at voice (210) 221-2511 (DSN 471-2511) or facsimile (210) 295-0244 (DSN 421-0244) during duty hours. After duty hours contact CIRO using digital pager (210) 613-1442. (AR 40-7, 4-9b)

i. CIRO will perform second-level review for all clinical investigation (CI) research studies and amendments that do not require CIRO approval. CIRO should receive all such studies and amendments from CI activities within 30 days of approval to begin the studies and implement the amendments. CIRO will review these studies and amendments within a reasonable time. CI activities will be notified of any required study or amendment revisions. (AR 40-38, 2-7b)

j. Reference the 5 Feb 94 memorandum entitled "Policy on the use of animals for medical purposes in U.S. Army Medical Command Programs" issued by MG Cameron, CIRO should receive approved IACUC minutes within 30 days of approval, animal protocols within 60 days of approval, and the USDA annual report by 1 Dec following the end of the report fiscal year (30 Sep). CIRO will review these studies and amendments within a reasonable time. CI activities will be notified of any recommended or required revisions.

k. CIRO is the approving authority for extramurally funded CI studies. Extramural funds are funds obtained from sources other than a military medical treatment facility (Program 8 funds), e.g., funds obtained from the Medical Research and Materiel Command, National Institutes of Health, or non-federal entities. Gifts for specific CI studies are not authorized, and non-federal study funding should be implemented by cooperative research and development agreement (CRADA). Extramurally funded studies submitted to CIRO will be reviewed within ten working days of receipt. The outcome of CIRO review will either be approval, disapproval, or request for revision. Properly revised studies will be expeditiously approved (ten working days or less) after receipt. (AR 40-38, 3-6b(3))

l. CIRO will perform second level review of research protocols when the HSRRB is acting as the IRB of record. CIRO should receive all such studies and amendments from the HSRRB within 30 days of board recommendation. CIRO will review these studies and amendments within ten working days of receipt. If the research study is found in compliance CIRO will concur with the HSRRB's recommendation. CIRO does not have approval authority.

m. Perform Staff Assistance Visits (SAVs) to MTFs engaged in research as appropriate.

n. Receive and review APRs from each MTF engaged in research. APRs are reconciled with CIRS database to ensure compliance with protocols being forwarded for review. (AR 40-38, 2-10c(3))

I. C. 2. CIRO's CRADA Responsibilities

CIRO is the approving authority for extramurally resourced Clinical Investigation Program (CIP) studies. (AR 40-38, 3-6b(3))

Extramural resources are funds, equipment, and personnel, obtained from sources other than the military medical treatment facility (MTF) where the study is conducted, e.g., funds obtained from the Medical Research and Materiel Command, National Institutes of Health, or non-federal entities. MTF CIP study funds are Program 8 funds. Gifts for specific CIP studies (i.e., conditional gifts) are not authorized, and non-federal CIP study funding will be implemented by a cooperative research and development agreement (CRADA) approved by CIRO. Federal funds that have been transferred to a non-federal intermediary to support a CIP study will require a CRADA.

CIRO, designated as a Federal Laboratory and approval authority, has negotiated Master CRADAs with regularly recurring collaborators. Approved statements of Work (SOWS) may be appended to

these master CRADAs in support of specific CIP studies. CIRO will only approve CRADA/SOWs to support officially approved (IRB and Command approval) research studies done at CIP MTFs. A CRADA/SOW may support a specific CIP study conducted at multiple Army MTFs, however, a CRDA/SOW may not support multiple CIP studies, even if closely related.

Resources provided for in a CRADA/SOW are to be used for direct support of the research study in question at the Army CIP facility stated in the agreement. Resources in the form of personnel, working at the facility, are required to be credentialed and privileged, depending on professional capacity. Accounting records are to be maintained as stated in the agreement or as appropriate. A CRADA/SOW will cease to exist when a supported research study is terminated or completed.

If a CRADA is received without an accompanying study protocol, the CRADA will be held until the study protocol is received.

Principal investigators (PI), while not a signatory of the CRADA/SOW, will be sent, via email, the final document for concurrence prior to issuance of an approval letter by this office. PIs will also be sent amendments requiring substantial changes (usually resources) for concurrence. Additionally, PIs will be sent and be required to return the Conflicts of Interest statement (**TAB A**)

PIs disclosing being compensated by the study sponsor for personal speaking engagements will be required to sign an MFR stating they will refrain from speaking for the study sponsor in an unofficial capacity for the duration of the study.

I. C. 3. CIRO's Animal Use Oversight Responsibilities

The Clinical Investigation Regulatory Office (CIRO) is the designated oversight office in the Army Medical Department Center and School. CIRO is responsible for oversight of all Army animal use programs within the Defense Health Program (DHP-Program 8), which consists of the Departments of Clinical Investigation at the Army's MTFs that have animal use programs and facilities. In addition, the CIRO VPM serves as consultant to the Joint Special Operations Medical Training Center (JSOMTC), Fort Bragg, NC.

The Veterinary Program Manager (VPM) is the final approval authority for animal use protocols involving dogs, cats, nonhuman primates and marine mammals conducted at Army MTFs. The facility commander has approval authority for all other species, but the CIRO VPM will review all protocols for regulatory compliance and provide suggestions for improvement and recommendations for changes as necessary.

Each facility is required to provide CIRO with a copy of the following documents:

a. All animal use protocols and corresponding IACUC minutes.

b. Semiannual IACUC facility and program review reports after IACUC approval.

c. Annual USDA report with a cover letter listing the number of rats and mice used, with the corresponding pain categories. This information is compiled for use in DA and DoD level briefings.

d. Annual Data Call information as requested by SAIC.

e. AAALAC Program Descriptions and all correspondence concerning AAALAC accreditation.

The VPM serves on the Joint Technical Working Group (JTWG) of the Armed Services Biomedical Research Evaluation and Management (ASBREM) Committee. The JTWG usually meets bi-monthly or quarterly, depending on issues pending. Attendance is generally by conference call or VTC.

The VPM is the technical advisor to the Attending Veterinarians at all Army MEDCEN DCIs, the AMEDDC&S, and the Joint Special Operations Medical Training Center at Fort Bragg for all issues concerning the proper use of animals in biomedical research and training.

Chapter II: Scope of CIRO'S Review Authority and Responsibility

II. A. Overview

These written policies and procedures establish the operational guidelines for effective functioning of the Army CIP in full compliance with the regulatory requirements of DoD and the US Army.

CIRO's mission is to assure compliance with federal regulations for protection of human medical research subjects and for responsible use of animals in medical research and training. The Army clinical investigation program (CIP) improves health care and facilitates graduate medical education, graduate dental education, and other professional health education by stimulation of scholarly endeavor, retention of faculty, and introduction of new technology.

II. B. Ethical Principles

Protections for human research subjects are primarily founded on the three basic principles of the Belmont Report (1979). These principles are: (1) respect for persons; (2) beneficence; and (3) justice. These fundamental principles for the protection of human research subjects are embodied in the Federal regulations at 32 CFR 219, also called the Federal Policy or the Common Rule.

II. C. Laws, Regulations Directives and Instructions

The CIRO operates under and ensures research activities are in compliance with Statutory Laws, Federal Regulations, DoD Directives, DoD Instructions, and Department of Army Regulations:

II. C. 1. Statutory Laws

10 USC 980: (last amended 2002) – Limitation on use of humans in research. This law states that the funds appropriated to the DoD may not be used for research involving a human being as an experimental subject unless:

(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 legal

representative of the subject, provided it is shown that participation in the research is intended to be beneficial to the individual subject.

Thus, if an investigator plans to enroll subjects who are not capable of providing their own informed consent, the investigator needs to demonstrate a clear intent to benefit each subject participating in the study.

This "intent to benefit" requirement often makes placebo-controlled clinical trials enrolling incapacitated individuals, incompetents, or minors problematic. Investigators must be able to articulate how their research intends to benefit individual subjects if the participants will be enrolled the placebo arm of the trial. For example, a subject in the placebo arm may benefit directly from medical treatment or increased surveillance provided because of the research that is beyond the standard of care.

Because both clauses mandate advance informed consent, 10 USC 980 has historically prevented the DoD from funding emergency research in which advance informed consent of subjects cannot be obtained (e.g., research involving new treatments for trauma victims), even if such research would otherwise have been in compliance with all other applicable laws.

The National Defense Authorization Act of 2002 amended 10 USC 980 to address this issue. The amendment permits the Secretary of Defense to waive the requirement for advance informed consent "with respect to a specific research project to advance the development of a medical product necessary to the armed forces if the research project may directly benefit the subject and is carried out in accordance with all other applicable laws." In DoD Directive 3216.2, the Secretary of Defense delegated this waiver authority to the Heads of DoD Components (e.g., Secretary of the Army).

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 HHS regulations.

10 USC 1107: Notice of use of an investigational new drug (IND) or a drug unapproved for its applied use (2 January, 2001) - Whenever the Secretary of Defense requests or requires a member of the Armed Forces to receive an IND or a drug unapproved for its applied use, the Secretary shall provide the member with notice containing the required information about the IND. The Secretary shall also insure that health care providers who administer an IND 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.

Waiver of informed consent for Force Health Protection (FHP): The requirement for prior informed consent in the use of INDs with the members of the Armed Forces may be waived for FHP only by the President of the United States under 10 USC 1107. The Secretary of Defense may make the request for a waiver of informed consent, and the waiver needs to be approved by the President of the United States.

II. C. 2. Federal Regulations

32 CFR 219: Protection of Human Subjects. This is identical to 45 CFR 46, Subpart A.

45 CFR 46: Subpart B: Additional Protections Pertaining to Research, Development, and Related Activities Involving Fetuses, Pregnant Women, and Human In Vitro Fertilization; Subpart C:

Additional Protections Pertaining to Biomedical and Behavioral Research Involving Prisoners as Subjects; and Subpart D: Additional Protections for Children involved as Subjects in Research.

21 CFR 50: Protection of Human Subjects (FDA)

21 CFR 54: Financial Disclosures by Clinical Investigators (FDA)

21 CFR 56: Institutional Review Boards (FDA)

21 CFR 312: Investigational New Drug Application (IND) (FDA)

21 CFR 812: Investigational Device Exemption (IDE) (FDA)

45 CFR 160 & 164: Health Insurance Portability and Accountability Act (HIPAA) of 1996 (HHS - Office for Civil Rights - HIPAA)

II. C. 3. DoD Directives (DoDD)

DoDD 3216.2: Protection of Human Subjects and Adherence to Ethical Standards in DoD-Supported Research: 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 6200.2: Use of INDs for Force Health Protection (FHP): This directive establishes guidance for compliance with FDA requirements for INDs, given at 21 CFR 312. The Secretary of the Army, as Executive Agent, in concert with the Commander of the Combatant Command involved and the Assistant Secretary of the Army for Health Affairs, develop a specific treatment protocol for use of the IND. These protocols must be approved by the HSRRB as a duly constituted IRB of Record under 21 CFR 56.

The only exceptions to the directive 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, for which the HSRRB is also the IRB of Record. Additional requirements for HSRRB review of these protocols, include the following: (1) the HSRRB must include at least three non-affiliated members, who are not employees of the Federal Government; (2) review shall take place at a meeting in which a majority of members are present, including, if feasible, a majority of the non-affiliated members ; (3) minutes shall be provided to the Secretary of Defense and the FDA; and (4) the HSRRB must review and approve the IND information sheet, the plan to disseminate information on the IND to potential recipients and healthcare providers, and the informed consent form as required by FDA regulations at 21 CFR part 50.

II. C. 4. DoD Instructions (DoDI)

Department of Defense Instruction (DoDI) 3210.7, "Research Integrity and Misconduct," 05/14/2004: SUMMARY: This Instruction supplements the policy established by paragraph 4.8. of DoD Directive 3216.2 and implements subparagraph 5.1.5. of DoD Directive 3216.2 by specifying detailed procedures and standards for the Department of Defense 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.

II. C. 5. Department of the Army (DA) Regulations

AR 40-38: refers to research conducted in the context of supporting postgraduate education programs at Army MTFs, for the advancement of medical science, and its military and nonmilitary application to patient care. This includes: biomedical research and behavioral studies involving human subjects; activities involving new drugs, vaccines, biologics, or investigational medical devices; and activities funded by both Army and non-Army resources in which subjects are DoD beneficiaries. Sets policies, procedures, and responsibilities for the participation of human subjects and the accountability for material and funds used in the Army CIP.

CIRO is granted review and in certain circumstances approval authority for all research within the Army CIP except specifically stated categories of research in AR 70-25 and AR 40-7.
AR 40-33; refers to live vertebrate animal that is being used or is intended for use in research, training, or testing, or for experimentation purposes. CIRO is granted approval authority when cats, dogs, or non-human primates are used.

II. C. 6. MEDCOM Policy

MEDCOM Policy on Use of Animals for Medical Purposes (6 February 1994)

This memorandum provides guidance for the use of animals in the Army Medical Command (MEDCOM) programs (non-MRMC). The MEDCOM will continue to use animals for clinical investigations, research, medical training, diagnostic procedures and toxicity testing.

The Army Medical Department Center and School (AMEDDC&S) Clinical Investigation Regulatory Office (CIRO) will provide oversight for all aspects of animal use and will monitor care and use programs for assurance of compliance with federal law and Army regulations.

II. D. Oversight and Compliance Review

II. D. 1. Oversight and Compliance Review of Army CIP Sites

CIRO is responsible to coordinate and monitor CIP activity and serve as the point of contact for policies and regulations on animal use, human use, and funding and administration of the Army CIP (Second-level review).

TSG has delegated DoD Assurance approval to ASG, FP. CIRO will prepare Assurance of Compliance documents from the Army Medical Department Regional Medical Commands and submits to the ASG, FP for approval. CIRO will prepare Assurances only for Army Regional Medical Commands (**TAB B**). Assurances expire **three years** from the date of their issuance or a change in the signatory official. Supporting documents must be updated subsequent to a change of Human Protections Administrator, the Chair, IRB, the IRB membership, or of the policies and procedures to maintain the file current. A revised and dated IRB membership roster must be submitted if there is a change in the IRB membership. For its uninterrupted continuation, Assurances must be resubmitted to CIRO prior to its expiration. Renewal will require submission to this office of the Department of Clinical Investigation (DCI)/Institutional Review Board (IRB) written policies and procedures (SOPs), IRB membership roster(s), Cooperative Agreement(s), if any, with other institutions regarding acceptance of IRB recommendations, and the Assurance document completed, signed and dated by the Human Protections Administrator and Institutional Official.

CIRO will use a variety of measures to oversee the CIP to assure compliance with federal regulations for protection of human medical research subjects and for responsible use of animals in medical research and training. These measures will include, but not limited to, review of individual Department of Clinical Investigation (DCI) /Institutional Review Board (IRB) written policies and procedures (SOPs), review of IRB minutes, review of IACUC minutes, review of all study protocols and consent forms, and reconciliation of annual progress reports (APR). Additionally, CIRO staff will conduct SAVs to MTFs CIP activities as appropriate, usually every 2 to 3 years. A SAV can occur anytime if deemed necessary by the Chief, CIRO.

Investigators at the MTFs submit studies to the local IRB for review. Administrative processing of these submissions by the local IRB begins with the determination of whether a study qualifies as research, and if so, whether:

(1) It is "exempt" from the regulatory requirements (32 CFR 219.101(b)); or

(2) It qualifies for review by the "expedited" procedure (32 CFR 219.110); or

(3) It requires "full board" IRB review (32 CFR 219.109).

Research in the first two categories above may begin upon a recommendation to approve from the local IRB and approval from the local Commander (AR 40-38) if no extramural funding is being used.

Note that in these three situations, the Commander may not overturn any stipulations, conditions, or requirements imposed on a study by the local IRB. The Commander may, however, impose additional requirements or restrictions on a study under his/her jurisdiction.

Materials for Review: CIRO is to receive and will electronically archive the following protocol-related documents for second-level compliance review:

(1) Protocol (signed by all investigators) in format consistent with AR 70-25 & 40-38.

(2) Consent forms (dated and stamped approved version).

(3) All investigator CVs and documentation of human subjects protection training.

(4) Medical monitor appointment letter for greater than minimal risk studies.

(5) Advertisements and other recruitment materials.

(6) Other documents as appropriate (e.g., Form FDA 1572, Investigator's brochure, etc).

(7) Study amendments.

(8) IRB documentation of continuing review.

(9) Reports of serious unexpected adverse event and/or unanticipated problems that are determined by the medical monitor to be possibly caused by the subject's participation in the clinical investigation protocol.

(10) IRB & IACUC documentation of suspensions or terminations.
(11) IRB & IACUC minutes.

IRB & IACUC minutes: Minutes are reviewed for compliance with regulations and policy. Examples of review items include identification of a quorum, panel membership, vote recording, proper determination of continuing review, medical monitor assignment (if applicable), adequate description of deliberations for type and complexity of research study, any special circumstances that may pertain to the research study (vulnerable population, 10USC980, etc) and final approval by the commander or designee.

Study protocols and consent forms: All study protocols and consent forms are reviewed for compliance with regulations and guidance. Examples of review items include documentation of scientific review (if applicable), signatures of principal and associate investigators, applicable impact statements, proper funding procedures (if any), 8th to 10th grade language used within the consent form, correct spelling and grammar, and consent form containing all requirements set forth in AR 40-38, appendix C.

Annual Progress Reports: APRs are reconciled against the CIRS database to ensure CIRO has received all protocols from the MTFs throughout the fiscal year. Additionally, determination is made to which protocols remain open, and which have been completed, or terminated.

II. D. 2. Oversight and Compliance Review of HSRRB as the IRB of Record

The HSRRB may function as the first level IRB of record for certain types of human subjects programs, e.g., use of INDs for FHP studies (DoD 6200.2); and any Army sponsored research not otherwise approved by an Army IRB. This board is the principle resource for OTSG in assuring implementation of the Federal requirements for the protection of human subjects in Army-sponsored, USAMRMC-managed research (10 USC 1107).

TSG is specifically designated to be the final approving authority for human subjects research in the following categories:

a. Studies involving human subjects using Schedule I controlled drug substances (AR 40-7);

b. Research involving minors or other vulnerable categories of human subjects, when subjects are wards of a state or other agency or institution (AR 70-25 (2-5.*g*));

c. Research proposals from major Army Commands (MACOMs) that do not have a HUC/IRB or other internal review process (AR 70-25 (2-5.*d*)).

d. Research involving Army's health hazard assessment program and health hazards of medical and non-medical materiel.

When the HSRRB functions as the IRB of record CIRO will perform a second level review for compliance with applicable human subjects regulations. Discrepancies or differences of opinion (e.g. interpretation of a regulation) that cannot be resolved will be reported to the HSRRB Institutional Official (MRMC Commander). If the research study is found in compliance, CIRO will concur with the HSRRB's recommendation. CIRO does not have approval authority.

Materials for Review: CIRO is to receive and will electronically archive the following protocol-related documents for second-level compliance review:

(1) Protocol (signed by all investigators) in format consistent with AR 70-25 & 40-38.

(2) Consent forms (dated and stamped approved version).

(3) All investigator CVs and human subjects protection training certificates.

(4) Protocol risk assessment and named medical monitor (and his/her CV) for greater than minimal risk protocols.

(5) Advertisements and other recruitment materials.

(6) Other documents as appropriate (e.g., Form FDA 1572, Investigator's brochure, etc).

(7) Study amendments.

(8) HSRRB documentation of continuing review.

(9) Reports of serious unexpected adverse event and/or unanticipated problems that are determined by the medical monitor to be possibly caused by the subject's participation in the clinical investigation protocol.

(10) HSRRB documentation of suspensions or terminations.

(11) HSRRB as IRB of Record minutes.

Additionally, CIRO will review and archive the following:

(1) HSRRB Policies and Procedures.

(2) HSRRB membership roster.

(3) HSRRB member orientation and continuing education scheme.

II. D. 3. DoD's and Army's "Unique" Review Requirements

In reviewing and when required approving, CIRO must also consider the following DoD's, and Army's unique issues in DoD sponsored research:

Certification of Translation - Provide documentation that the foreign language version of the consent form is an accurate translation.

Sample Donation - If the samples donated in this study will be used in other studies, an approved DoD statement for this purpose should be included in the consent form:

Payment for Study Participation: Active Duty Military Personnel - Under 24 USC 30, payment to Active Duty military personnel for participation in research is limited to blood donation and may not exceed $50 per blood draw. Active duty research subjects may not receive any other payment for participation in a research study.

Confidentiality - The following statement must be included in the consent form for all protocols that enroll military personnel:

"All data and medical information obtained about you, as an individual, will be considered privileged and held in confidence; you will not be identified in any presentation of the results. Complete confidentiality cannot be promised to subjects, particularly to subjects who are military personnel, because information bearing on your health may be required to be reported to appropriate medical or command authorities."

Pregnant Women - If pregnant women will be excluded, the following statement must be included in the consent form if pregnancy during or after the study constitutes a risk to the participant or fetus:

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

Requirement for an Ombudsman - CIRO will give special consideration to the recruitment process for military personnel. During recruitment briefings to a unit where a percentage of the unit is being recruited to participate as a group, an **ombudsman,** not connected in any way with the proposed research or the unit, shall be present to monitor that the voluntary nature of individual participants is adequately stressed and that the information provided about the research is adequate and accurate. (DoDD 3216.2, Paragraph 4.4.4.) For research involving more than minimal risk and also involving military personnel, unit officers and noncommissioned officers (NCOs) may not influence the decisions of their subordinates to participate or not to participate as research subjects. Unit officers and senior NCOs in the chain of command may not be present at the time of research subject solicitation and consent during any research recruitment sessions in which members of units under their command are afforded the opportunity to participate as research subjects. When applicable, officers and NCOs so excluded shall be afforded the opportunity to participate as research subjects in a separate recruitment session. (Department of Defense Directive (DoDD) 3216.2, Paragraph 4.4.4.) Soldiers are trained to act as a unit, so peer pressure should also be considered and minimized if possible.

Limitation on the Use of Humans as Experimental Subjects - Title 10 United States Code 980 requires that "Funds appropriated to the Department of Defense may not be used for research involving a human being as an experimental subject unless - (1) the informed consent of the subject is obtained in advance; or (2) in the case of research intended to be beneficial to the subject, the informed consent may be obtained from a legal representative of the subject."

Furthermore and consistent with the Federal Policy for the Protection of Human Subjects, if an individual cannot give his/her consent to participate in a research study, consent of the individual's legally authorized representative must be obtained prior to the individual's participation in the research. Moreover, an individual not legally competent to consent (e.g., incapacitated individuals, incompetent individuals, minors) may not be enrolled in DOD sponsored research unless the research is intended to benefit each subject enrolled in the study.

For studies in which there is a plan to include subjects that are not capable of providing their own consent, the IRB must determine that there is an intent to benefit each subject that will be enrolled in the trial

Requirement for a Medical Monitor - Per DOD Directive 3216.2, all greater than minimal risk studies require a medical monitor. The IRB will ensure that an appropriate individual is assigned with an appointment letter. The appointment letter must be included in the protocol packet sent to CIRO for review.

This individual should be a qualified physician, other than the Principal Investigator, not associated with the protocol, able to provide medical care to research volunteers for conditions that may arise during the conduct of the study, and who will monitor the volunteers during the conduct of the study. In some studies it may be acceptable to have a qualified health care provider other than a physician serve as medical monitor, depending upon the type of risk that might occur in the study (e.g. a clinical psychologist). The medical monitor plays a role in reviewing serious adverse events and unanticipated problems prior to submission to the CIRO. The CIRO will review the proposed role of the medical monitor in protocol and determine if it allows the medical monitor to remain independent from the study.

II. D. 4 Staff Assistance Visits (SAVs)

CIRO carries out periodic on-site Staff Assistance Visits (SAVs) to institutions where AMEDD CIP non-exempt human subject research is conducted. Where on-site visits are not practical, the assigned medical monitor will be specifically asked to check the investigator's records for signed consent documents, patients' meeting eligibility criteria, proper administration of test agents, reporting of serious adverse events and other unanticipated problems, patient withdrawals, etc. Schedules for these visits will be prioritized according to the urgency of the need for assistance and oversight.

A Staff Assistance Visit may include the following activities:

(1) Reviewing local IRB's Policies and Procedures

(2) Reviewing local IRB's minutes

(3) Reviewing selected protocols and consent forms.

(4) Conducting interviews with local IRB members

(5) Conducting interviews with investigators

(6) Conducting interviews with institutional officials

(7) Examining the placement of the Human Subjects Protection Program in the organizational chart

Chapter III: Protocol Categories for Review of Compliance

III. A. Exempt

Certain research involving human subjects is exempt from the IRB review requirements of 32 CFR 219, and AR 40-38. For the categories of research that are exempt from the Federal regulations, refer to 32 CFR 219.101(b) and AR 40-38, Appendix B. Department or agency heads may make the final determination of whether a given research protocol is exempt (32 CFR 219.101(c)).

Investigators who intend to involve human subjects in research **will not** make the final determination of exemption from applicable Federal regulations. Investigators will rely upon their institutions IRB to make the determination of exemption prior to initiating the research.

Upon the IRB's recommendation and the local Commander's approval, a protocol that has been determined to be exempt may commence and the protocol is to be forwarded to CIRO for review. CIRO will review the protocol for regulatory compliance, but make no correspondence unless non-compliance is noted or extramural funding is used.

III. B. Expedited

III. B. 1. Criteria for Review by "Expedited" Procedure

An expedited review procedure consists of a review of research involving human subjects by the IRB Chairperson, or by one or more experienced reviewers designated by the Chairperson from among members of the IRB, in accordance with the requirements set forth in 32 CFR 219.110. The IRB is required to keep all IRB members advised of research proposals that have been approved under the expedited review procedure. 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 IRB in accordance with the procedure at 32 CFR 219.108(b). Under 32 CFR 219.110(d), OTSG may restrict an institution's or IRB's authority to use the expedited review procedure.

III. B. 2. Nine Categories of Research approvable by Expedited Review

The list of categories of research that may be reviewed by the IRB through an expedited review procedure was updated in 1998 and can be found at the following website: http://www.hhs.gov/ohrp/humansubjects/guidance/expedited98.htm. The **nine research categories that may be managed by expedited review** are quoted below:

> **"Category (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 312) is not required. (Note: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.)

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

Category (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, 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.

Category (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 gum base or wax or by applying a dilute citric solution to the tongue; (f) placenta removed at delivery; (g) amniotic fluid obtained at the time of rupture of the membrane prior to or during labor; (h) supra- and sub-gingival 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.

Category (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.

Category (5): Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical

treatment or diagnosis). (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.)

Category (6): Collection of data from voice, video, digital, or image recordings made for research purposes.

Category (7): Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. (NOTE: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(2) and (b)(3). This listing refers only to research that is not exempt.)

Category (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.

Category (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."

Additions to, and extrapolation from, this list by the institution or the IRB are not appropriate. For example, it is inappropriate to use an expedited review procedure for the initial review of either research that involves minimal risk but does not appear in the categories of research published in the Federal Register or research that involves greater than minimal risk.

III. B. 3. Use of Expedited Review Procedure by an IRB

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

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

(2) **minor changes in previously approved research** during the period of one year or less for which approval is authorized (32 CFR 219.110; 21 CFR 56.110; AR 40-38, 3-5.g. and Appendix H). Minor changes in approved research covers the following situations:

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

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

CIRO will review expedited protocols for regulatory compliance providing suggestions for improvement and noting required changes as necessary. CIRO approval, if required, will be issue upon completion of the required changes.

III. C. Research Requiring Full IRB Review

CIRO will review protocols reviewed by a CIP IRB for regulatory compliance providing suggestions for improvement and noting required changes as necessary. CIRO approval, if required, will be issue upon completion of the required changes.

Chapter IV: Unanticipated Problems and AEs, Serious or Continuing Noncompliance and Suspension or Termination of IRB Approval

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

The events that need to be reported to the IRB are given 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)).

IV. A. Unanticipated Problems and Adverse Events

Unanticipated problems are those problems that are not described in the protocol or other study documents. The IRB of record will decide if these reported events are truly part of the risks of daily living or routine medical care and thus implicitly anticipated. The criteria for whether such occurrences need to be acted on and perhaps reported to the Department or other authorities are the same as for any serious adverse events (SAEs) or traditional safety report (32 CFR 219.103(b)(5)(i)); (21 CFR 56.108(b)(i)).

"Unanticipated Problems involving Risks to Subjects or Others" is a broader category than SAEs, and may include issues other than adverse drug reactions, such as problems with overdosing or drug abuse, loss of control of research agents, patient data, or hazardous materials, psychological reactions, risk of breach of confidentiality, economic risks, less than ideal results of treatment, etc. Risks to others must also be **reported.** For example, an inadvertent exposure of a household contact in a smallpox vaccine trial would be a **reportable** event. Problems resulting in risks to members of the research team are also **reportable.**

The only regulatory citation regarding **reporting** of adverse events (AEs) to the IRB is given at 21 CFR 812.150(a)(1). It states that an investigator shall submit to the sponsor and to the reviewing IRB a **report** of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.

Therefore, theoretically, the IRB does not have to receive AE reports other than those that fall under 32 CFR 219.103(b)(5)(i) and 21 CFR 56.108(b)(1), regarding any unanticipated problems involving risks to subjects or others.

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)). What this means is that the IRB may require the investigator to evaluate all adverse events to ensure the safety of the subjects.

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

IV. B. Reporting Responsibilities of the Principal Investigator

The PI needs to immediately notify the local Commander/Institutional Official through the medical monitor and the IRB of adverse effects or any unanticipated problems involving risks to subjects or others caused by the CI as required at 32 CFR 219.103(b)(5), AR 40-38 2-10c(5) and, comply with any other site specific reporting requirements.

Prospective Inspection of Intramural Research by an Outside Governmental Agency: As soon as a PI learns of a prospective compliance inspection, site-visit or audit by another Government Agency, e.g., FDA, OHRP, etc., of any intramural research, s/he should immediately inform the Chairperson, IRB. Additionally, notify CIRO by telephone (DSN 471-2511 or 210-221-2511)

IV. C. Reporting Responsibilities of the Medical Monitor

The medical monitor is required to review all unanticipated problems involving risk to subjects or others, serious or life-threatening adverse events related to participation in the study, and all subject deaths associated with the protocol, and provide an unbiased written report of the event. At a minimum, the medical monitor should comment on the outcomes of the event or problem, and in the case of an adverse event or death, comment on the relationship to participation in the study. The medical monitor should also indicate whether s/he concurs with the details of the report provided by the study investigator.

IV. D. Reporting Responsibility of the Local IRB

Evaluating instances of apparent investigator noncompliance, and recommending remedial actions, such as education and operational improvements or applicable sanctions, are the responsibility of the local IRB. Each IRB shall adopt policies to provide for such deliberations. These policies shall distinguish between minor and major violations, shall provide for systematic evaluations of incidents and possible appeals, and will outline possible actions and notifications of higher officials of DA and other Institutions.

Upon being notified by a PI of an unanticipated problem involving risks to subjects or others, the IRB will ensure the medical monitor is aware of the event and performs a review as outlined in the medical monitor responsibilities.

In an effort to fulfill the CIRO's responsibility for monitoring and oversight of research, CIRO requires that all serious or life-threatening, research-related, adverse events and all subject-deaths, be reported to CIRO if determined by the medical monitor to be possibly caused by the subject's participation in the clinical investigation protocol. Reports are to be submitted by telephone NLT the next duty day to CIRO (210-221-2511). A written report is to follow the initial telephone call within 3 working days.

IV. E. Suspension or Termination of IRB's Approval

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

Any suspension or termination of a protocol shall be communicated to CIRO by the institutions IRB within one week suspension or termination. If the research involves an IND or IDE, or the funds supporting the research come from another Federal Department or agency, the appropriate officials at FDA and/or OHRP (if HHS sponsorship is also involved), etc., shall also be notified by the IRB at the same time. Such suspensions or terminations will be reported to DDR&E by CIRO.

Chapter V: CIRO's Monitoring and Quality Assurance Programs

Protection of human subjects in research starts with a written institutional commitment (i.e., a DoD Assurance of Compliance or a Federal-Wide Assurance), promulgation of institutional policies and guidelines, and education on IRB's written policies and procedures. In addition to these mandates, a proactive human subjects 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.

V. A. Medical Monitors

Medical Monitor: DoDD 3216.2 requires that in research funded by the DoD involving more than minimal risk to subjects, an independent medical monitor must be appointed by name. Medical monitors shall be physicians, dentists, psychologists, nurses, or other health care providers capable of overseeing the progress of research protocols, especially issues of individual subject/patient management and safety. Medical monitors shall be independent of the investigative team and shall possess sufficient educational and professional experience to serve as the subject/patient advocate. Depending on the nature of the study, the medical monitor may be assigned to assess one or more of the following phases of a research project: subject recruitment, subject enrollment, data collection, or data storage and analysis. At the discretion of the IRB, the medical monitor may be assigned to discuss research progress with the PI, interview subjects, consult on individual cases, or evaluate adverse event reports. Medical monitors shall promptly report discrepancies or problems to the IRB. They shall have the authority to stop a research study in progress, remove individual subjects from a study, and take whatever steps are necessary to protect the safety and well-being of research subjects until the IRB can assess the medical monitor's report (DoDD 3216.2, Paragraph 4.4.3.).

V. B. CIRO's Quality Assurance Program

As per the Army Human Subjects Research Protection Management Plan, CIRO requires that all personnel connected with the human subjects research review process, institutional officials, IRB members, administrative staff, investigators, etc. undergo appropriate training to meet their obligation to protect the rights and welfare of human subjects.

CIRO's Quality Assurance includes:

(1) first, assuring that all individuals engaged in supporting, reviewing or conducting human subjects research meet at least the minimum regulatory education and training requirements of DoD and its components; and

(2) second, striving to go beyond meeting the minimal requirements and seeking to implement as high ethical standards to all human subjects research as possible under the circumstances.

These programs aim to achieve a high level of compliance in assuring protection of human research subjects through education and training. Preventing, finding, and overcoming episodes of noncompliance are among the specific minimal objectives of the Quality Assurance program. Quality Improvement involves taking steps that enhance protections for the rights and welfare of the human research subjects beyond the minimal regulatory requirements.

Among the web-based free training programs available are the following:

(1). Website at the OHRP: http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp This website has the following three training modules: (a). HHS Regulations & Institutional Responsibilities; (b). Investigator Responsibilities & Informed Consent; (c). Human Research Protections Program;

(2). Website at the National Cancer Institute (NCI) for on-line training: http://cme.cancer.gov/clinicaltrials/learning/humanparticipant-protections.asp

IRBs are encouraged to engage in comprehensive local self-assessment of their Quality Assurance and Quality Improvement Programs. Local performance sites may utilize evaluation and education visits by consultants, IRB staff / members from other institutions, and utilize available guidance, tools or checklists, such as those available from the FDA and OHRP.

Chapter VI: CIRO Records

VI. A. Types of Records

CIRO records consist of copies of documents submitted by Army CIP IRBs for review and correspondences between CIRO and the IRBs . These documents include but are not limited to: protocols, informed consent documents, transmittal letters, IRB minutes, IACUC minutes, investigator brochures, investigator CVs, CIRO's review findings, APRs, and DoD Assurance documentation.

VI. B. Security of Records

(1). All CIRO records will be kept securely in locked storage rooms, locked filing cabinets, or in restricted computer files. Access is ordinarily limited to the CIRO staff.

(2). 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.

(3). In addition, other individuals and groups may legitimately obtain copies of particular documents or, exceptionally, have access to files, if determined by Chief, CIRO, to be appropriate. This may include investigators, representatives from cooperative research groups, officials from FDA and other federal agencies as determined by law and regulations, and private individuals requesting copies of documents under applicable Freedom of Information (FOI) laws. If rights of access are at all unclear, the Chief, CIRO will consult Judge Advocate for the General (JAG).

VI. C. Retention of Records

CIRO will electronically archive all records stored in Adobe Acrobat PDF on a master office hard drive with nightly duplication to several other office hard drives to prevent data loss. Additionally, all records will be burned to DVD by fiscal year.

Chapter VII: Periodic Updating of CIRO's Written Policies and Procedures

CIRO shall regularly review its written Operational Policies and Procedures, and modify these as necessary to conform with or exceed current moral, ethical, and legal standards, no less often than once every year. This document will be shared with the Army CIP members for their input, prior to its approval by the Chief, CIRO.

TAB A

MEMORANDUM FOR Chief, Clinical Investigation Regulatory Office, AMEDDC&S, ATTN: MCCS-GCI, Fort Sam Houston, Texas 78234

SUBJECT: Certification of No Financial Conflicts of Interest

1. I certify that I am the Principal Investigator on the CRADA-funded research study entitled:

_____

_____

2. All of the following statements are true (mark as applicable). If any of the following statements are not true, then I have explained the facts in paragraph 3. below.

T F Neither I, my spouse, nor dependent children have any financial interests in the overall study sponsor on this protocol.

T F Neither I, my spouse, nor dependent children have received or will receive any gratuity, gift, or compensation from the overall study sponsor on this protocol.

T F Neither I, my spouse, nor dependent children are employed by, or have an agreement for future employment with, the overall study sponsor on this protocol.

T F Neither I, my spouse, nor dependent children hold any position as an officer, director, trustee, partner, proprietor, representative, executor, or consultant with the overall study sponsor on this protocol.

3. _____

_____

_____

_____

(If more room is needed, continue on the back of this page.)

_____
(Principal Investigator Signature)

_____
(Typed/Printed Principal Investigator Name)

_____ (Date)

TAB B

DOD's MULTIPLE PROJECT ASSURANCE (MPA) OF COMPLIANCE FOR THE PROTECTION OF HUMAN SUBJECTS

North Atlantic Regional Medical Command

North Atlantic Regional Medical Command, hereinafter known as the "Institution," hereby gives assurance that it will comply with the Department of Defense (DoD) regulations for the Protection of Human Subjects (32 CFR 219); Title 10, United States Code, Section 980, Limitation on Use of Humans as Experimental Subjects (hereinafter referred to as 10 USC 980); DoD Directive 3216.2; AR 40-38; AR 70-25; and where applicable, 21 CFR 50, 21 CFR 56, and 45 CFR 46 (Subparts B, C, and D) under the authority of the DoD.

Components of the Institution:

North Atlantic Regional Medical Command

Departments of Clinical Investigation:	Walter Reed Army Medical Center
Womack Army Medical Center	
Keller Army Community Hospital	
Institutional Review Boards (IRBs):	Walter Reed Army Medical Center
Military Cancer Institute	
Womack Army Medical Center	
Keller Army Community Hospital	
Medical Treatment Facilities:	Walter Reed AMC, Washington, DC
Womack AMC, Ft. Bragg, NC	
Keller ACH, West Point, NY	
DeWitt ACH, Ft. Belvoir, VA	
Rader AHC, Ft. Myer, VA	
DiLorenzo TRICARE Health Clinic, Pentagon, VA	
Ireland ACH, Ft. Knox, KY	
McDonald ACH, Ft. Eustis, VA	
Kimbrough ACC, Ft. Meade, MD	
Guthrie AHCC, Ft. Drum, NY	
Kenner AHC, Ft. Lee, VA	
Patterson AHC, Ft. Monmouth, NJ	

PART 1

Ethical Principles and Institutional Policies Governing Research Involving Human Subjects

I. Applicability

Except when research is exempt from the requirements of 32 CFR 219, or applicability of 32 CFR 219 is waived under 32 CFR 219.101, this Assurance applies to all research involving human

subjects, and all other activities which involve such research even in part, regardless of whether the research is otherwise subject to federal regulation, if:

A. the research is sponsored by this Institution,

B. the research is conducted by or under the direction of any employee or agent of this Institution in connection with Institutional responsibilities,

C. the research is conducted by or under the direction of any employee or agent of this Institution using any property or facility of this Institution, or

D. the research involves the use of this Institution's nonpublic information to identify or contact human research subjects or prospective subjects.

II. Ethical Principles

This Institution assures that all of its activities related to human subject research will be guided by the ethical principles set forth in the Nuremberg Code and the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled, Ethical Principles and Guidelines for the Protection of Human Subjects of Research (the "Belmont Report").

A. This Institution recognizes the principles of respect for persons, beneficence (including minimization of harms and maximization of benefits), and justice as stated in the Belmont Report, and will apply these principles in all research covered by this Assurance.

B. This Institution acknowledges and accepts its responsibilities for protecting the rights and welfare of human research subjects.

III. Policies

A. This Institution acknowledges that it and its investigators bear full responsibility for the performance of all research covered by this Assurance, including full responsibility for compliance with Federal, State, and local laws as they apply to such research.

B. This Institution assures that before human subjects are involved in research, proper consideration will be given to:

1. the risks to the subjects,

2. the anticipated benefits to the subjects and others,

3. the importance of the knowledge that may reasonably be expected to result,

4. the informed consent process to be employed, and

5. the provisions to protect the privacy of subjects.

C. This Institution recognizes the need for appropriate additional safeguards in research involving subjects who are likely to be vulnerable to coercion or undue influence, such as children, prisoners, pregnant women, mentally disabled persons, military personnel, or economically or educationally disadvantaged persons.

D. This Institution encourages and promotes constructive communication among the Institutional officials, research administrators, department heads, research investigators, clinical care staff, human subjects, and all other relevant parties as a means of maintaining a high level of awareness regarding the safeguarding of the rights and welfare of the subjects.

E. This Institution will exercise appropriate administrative overview, carried out at least annually, to ensure the effective application of its practices and procedures designed for the protection of the rights and welfare of human subjects.

F. Federal funds for research involving human subjects, to which this Assurance applies, may not be expended unless the requirements of this Assurance have been satisfied.

G. Certification of IRB review and approval and approving official approval will precede accrual of human subjects in research involving human subjects to which this Assurance applies.

H. When research covered by this Assurance is conducted at or in cooperation with another institution, this Institution will ensure that the other institution has obtained approval of an appropriate Assurance of Compliance prior to accrual of human subjects in such research.

I. When research covered by this Assurance is conducted at or in cooperation with another institution, this Institution may accept, for purposes of meeting the IRB review requirements, the review by an IRB established under another DoD-MPA. Such acceptance must be in writing and approved by appropriate officials of both institutions (Authorization Agreement).

PART 2

Responsibilities

I. Institutional Responsibilities

A. This Institution acknowledges that it bears full responsibility to comply with the requirements of 32 CFR 219, 10 USC 980, AR 40-38, AR 70-25, DoDD 3216.2, 21 CFR 50, 21 CFR 56, and 45 CFR 46 (Subparts B, C, and D) under the authority of the DoD, and other Federal, State, and local laws as they relate to human subjects research.

B. In accordance with the compositional and quorum requirements of 32 CFR 219.107-108, the IRB(s) designated in the components of the Institution (page 1) and in the attached roster(s) is (are) responsible for the initial and continuing review of research studies conducted under this

Assurance. This Institution will notify the Clinical Investigation Regulatory Office and update the Assurance file if there are changes to IRB membership.

C. This Institution will ensure that designated IRBs have sufficient space and staff to support the review and record keeping duties.

D. This Institution and the designated IRB(s) have established written procedures for:

1. verifying whether proposed activities qualify for exemption from IRB review,

2. conducting IRB initial and continuing review (not less than once per year) of research, and reporting IRB findings to the investigator and the approving official,

3. determining which projects require review more often than annually, and which projects need verification from sources other than the investigator that no material changes have occurred since previous IRB review,

4. ensuring that changes in approved research are reported promptly and are not initiated without IRB and approving official approval, except when necessary to eliminate apparent immediate hazards to subjects, and

5. ensuring prompt reporting to the IRB, Institutional officials, the relevant Department or Agency Head, and any applicable regulatory body, of any

(a) unanticipated problems involving risks to subjects or others in any covered research,

(b) serious or continuing noncompliance with Federal, Institutional, or IRB requirements, or

(c) suspension or termination of IRB approval of the DoD-supported research.

E. The Institutional Signatory Official, the Human Protections Administrator, and the IRB Chairperson(s) will complete the human subjects protection and assurance training prior to submitting this Assurance (use the training at http://ohrp-ed.od.nih.gov/CBTs/Assurance/login.asp). Members and staff of the IRB will complete appropriate training before reviewing human subject research. Research investigators will complete appropriate training before conducting human subject research.

F. This Institution and the designated IRB(s) have established education and oversight mechanisms (appropriate to the nature and volume of its research) to verify that research investigators, IRB members and staff, and other appropriate personnel maintain continuing knowledge of, and comply with, Federal regulations, other applicable guidance, State and local law, and Institutional policies for the protection of human subjects. The Institution and the designated IRB(s) will require documentation of such training from research investigators as a condition for conducting DoD-supported human subject research.

G. Any designation of an IRB not administered by the Institution must be documented by a written agreement (Authorization Agreement) between the Institution and the IRB organization outlining their relationship and including a commitment that the designated IRB will adhere to the requirements of this Assurance.

H. This Institution is responsible for ensuring that all institutions and investigators collaborating in its DoD-supported human subject research operate under an appropriate Assurance of Protection for Human Subjects. All institutions engaged in such research, including subcontractors and subgrantees, must hold their own Assurance.

I. This Institution will renew this Assurance every 36 months, even if no changes have occurred, in order to maintain an active Assurance. Failure to renew this Assurance will result in termination of the Institution's Assurance of Protection for Human Subjects.

II. Institutional Review Board Responsibilities

A. The IRB will review and must approve all research activity conducted under this Assurance, and any proposed changes to such research activity, before human subjects may be involved.

B. The IRB has the authority to require modification to or disapprove research activity conducted under this Assurance.

C. The IRB will determine, in accordance with the criteria found in 32 CFR 219.111, and where applicable, 45 CFR 46 (Subparts B, C, and D), that protections for human research subjects are adequate.

D. The IRB has the authority to suspend or terminate approval of research activity in accordance with 32 CFR 219.113 because of

1. noncompliance with 32 CFR 219, this Assurance document, or the IRB's requirements, or

2. unexpected serious harm to subjects.

E. The IRB will determine that legally effective informed consent will be obtained for all research in a manner which meets the requirements of 32 CFR 219.116-117.

F. The IRB will conduct continuing review of all research at intervals appropriate to the degree of risk, but not less than once per year [32 CFR 219.109(e)]. The IRB may be called into an interim review session by the Chairperson at the request of any IRB member or Institutional Official to consider any matter concerned with the rights and welfare of any subject.

G. The IRB will prepare and maintain adequate documentation of its activities in accordance with 32 CFR 219.115.

H. The IRB will report promptly to Institutional Officials and the Clinical Investigation Regulatory Office

1. any serious or continuing noncompliance by investigators with the requirements of the IRB,

2. any suspension or termination of IRB approval,

3. any unanticipated problems or injuries involving risks to subjects or others, or

4. any changes in research activities which are reviewed and approved by the IRB.

I. Where appropriate, the IRB will determine that adequate additional protections are implemented for fetuses, pregnant women, prisoners, and children as required by 45 CFR 46, Subparts B, C, and D, and if applicable, 10 USC 980. The IRB will notify the Clinical Investigation Regulatory Office promptly when IRB membership is modified to satisfy the requirements of 45 CFR 46.304 and when the IRB fulfills its duties under 45 CFR 46.305.

J. The IRB will comply with 10 USC 980, which states that if an individual cannot give his/her own consent (for example, minors), and there is no intent to benefit the individual, he/she cannot be entered into a study funded by the DoD.

III. Research Investigator Reporting Responsibilities

A. Investigators will acknowledge and accept their responsibility for protecting the rights and welfare of human research subjects and comply with all applicable provisions of this Assurance including 32 CFR 219; 10 USC 980; AR 40-38; AR 70-25; DoDD 3216.2; where applicable 21 CFR 50, 21 CFR 56, and 45 CFR 46 (Subparts B, C, and D) under the authority of the DoD; and other Federal, State, and local laws as they may relate to proposed human subjects research.

B. An investigator who intends to involve human subjects in research will not make the final determination of exemption from applicable Federal regulations or provisions of this Assurance.

C. Investigators are responsible for providing a copy of the IRB approved informed consent document to each subject at the time of consent, unless the IRB has specifically waived this requirement.

D. Research investigators will report promptly to the IRB any proposed changes to research activity. The changes will not be initiated without IRB review and approval, except where necessary to eliminate apparent immediate hazards to the subjects.

E. Research investigators will report promptly to the IRB any unanticipated problems involving risks to subjects and others.

IV. Additional Requirements

A. Supporting document to be submitted with this Assurance:

1. Human Protections Administrator appointment letter,

2. written policies and procedures (SOPs) for each IRB,

3. IRB Roster(s), and

4. any Authorization Agreements with other institutions regarding acceptance of IRB recommendations.

PART 3

Institutional Endorsement

The officials signing below assure that all research activities at this Institution will be conducted in accordance with the requirements of 32 CFR 219; 10 USC 980; AR 40-38; AR 70-25; DoDD 3216.2; and where applicable 21 CFR 50, 21 CFR 56, and 45 CFR 46 (Subparts B, C, and D) under the authority of the DoD; and this Assurance document. A roster listing the current membership of each designated IRB is attached at the end of this document.

I. Authorized Official of the Institution Providing This Assurance

The Signatory Official must be a senior Institutional Official who has the authority to commit the entire Institution named in the Assurance application, as well as all of the Institutional components to a legally binding agreement. Entities that the Signatory Official is not legally authorized to represent may not be covered under the Assurance. This individual must also have the authority to assure compliance of the Institution and all of its components to the terms of the Assurance. The IRB Chair and IRB members are not appropriate personnel to serve as the Signatory Official.

Signature: _____ Date: _____

Kenneth L. Farmer, Jr.
Major General, Medical Corps
Commander, North Atlantic Regional Medical Command
6900 Georgia Avenue, NW
Washington, DC 20307-5001
Voice: 202-782-1104
Email: Kenneth.Farmer@amedd.army.mil

II. Human Protections Administrator

Signature: _____ Date: _____

Maria H. Sjogren
Colonel, Medical Corps
Chief, Department of Clinical Investigation
MCHL-CI, 6900 Georgia Avenue, NW
Washington, DC 20307-5001
Voice: 202-782-6389
Fax: 202-782-3881
Email: Maria.Sjogren@amedd.army.mil

DEPARTMENT OF DEFENSE
*Multiple Project Assurance (MPA) Number: DoDXXXXX

North Atlantic Regional Medical Command

All parts of this Assurance are in compliance with requirements of 32 CFR 219, 10 USC 980, AR 40-38, AR 70-25, DoDD 3216.2, and where applicable, 21 CFR 50, 21 CFR 56, and 45 CFR 46 (Subparts B, C, and D) under the authority of the DoD.

DoD Approving Official

Signature: _____ Date: _____

Philip Volpe
Colonel, Medical Corps
Assistant Surgeon General, Force Projection
Office of the Surgeon General
5109 Leesburg Pike
Falls Church, VA 22041
Voice: 703-693-5601
Email: Philip.Volpe@otsg.amedd.army.mil

*Expiration Date:_____

*This assurance expires **three years** from the date of its approval or a change in the Institutional Signatory Official. Supporting documents must be updated subsequent to a change of the Human Protections Administrator, the IRB Chair, or of the policies and procedures to maintain this MPA file current. A revised and dated IRB membership roster must be submitted if there is a change in the IRB membership. For its uninterrupted continuation, this Assurance must be renewed with the Clinical Investigation Regulatory Office prior to its expiration.

INSTITUTIONAL REVIEW BOARD MEMBERSHIP

North Atlantic Regional Medical Command, Washington, DC
DATE: 1 April 2005
IRB of Record located at:
Walter Reed Army Medical Center

DoD Assurance Number _____

Rank/Title	Last Name	First Name	MI	Gender (M/F)	Affiliated (Y/N)	Earned Degrees	Professional Expertise
Primary Members							
IRB/HUC Chair 1.							
2.							
3.							
4.							
5.							
6.							
7.							
8.							
9.							
10.							
11.							
Alternates for Primary Members							
Rank/Title	**Last Name**	**First Name**	**MI**	**Gender (M/F)**	**Affiliated (Y/N)**	**Earned Degrees**	**Professional Expertise**	**Alternate for Member (Name/Number)**
12.								
13.								
14.								
15.								
16.								

Each IRB will have at least five members. Every nondiscriminatory effort will be made to ensure that this IRB does not consist entirely of men or entirely of women. No IRB may consist entirely of members of one profession. No IRB may have a member participate in review of any project in which the member has a conflicting interest. Each IRB will include at least one member with scientific expertise in the area of research being reviewed and one member with nonscientific background. Under **Affiliated**, please indicate (Yes or No) whether an individual is affiliated with the Institution or not. At least one member must not be affiliated with the Institution (32 CFR 219.107)