

Army Regulation 40-38

Medical Services

Clinical Investigation Program

**Headquarters
Department of the Army
Washington, DC
1 September 1989**

Unclassified

SUMMARY of CHANGE

AR 40-38

Clinical Investigation Program

This revision adds--

- o Authorization for major Army commanders to establish clinical investigation programs (chap 2).
- o Funding accountability in clinical investigation programs (chap 3).
- o An updated DA Form 5303-R, Volunteer Agreement Adffidavit.

Effective 2 October 1989

Medical Services

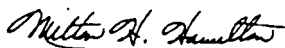
Clinical Investigation Program

By Order of the Secretary of the Army:

CARL E. VUONO

General, United States Army
Chief of Staff

Official:



MILTON H. HAMILTON
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History. This UPDATE printing publishes a revision of this publication. This publication has been reorganized to make it compatible with Army electronic publishing database. No content has been changed.

Summary. This regulation implements Department of Defense Directive (DODD) 3216.2 and DODD 6000.8. It reflects the present legal requirements pertaining to the use of human subjects participating in clinical investigations (CIs) and provides guidance for the administration and funding of clinical investigation programs (CIPs). Excluding situations where approval authority is limited, the authority to approve CIs using human subjects can be delegated within the

military chain of command to the lowest level operating a human subjects review process. This revision also prescribes the unchanged annual progress report (Clinical Investigation Program, RCS MED-300(R1)).

Applicability. This regulation applies to all Active Army medical treatment facilities (MTFs) and dental treatment facilities (DTFs) except those funded under research, development, test, and evaluation (RDTE) appropriations. (See AR 70-25 for guidance on RDTE funded activities.) This regulation does not apply to the U.S. Army Reserve (USAR) and the Army National Guard (ARNG) unless Active Army personnel are involved.

Proponent and exception authority. Not applicable

Army management control process. This regulation is subject to the requirements of AR 11-2. It contains internal control provisions but does not contain a checklist for conducting internal review. Checklists are being developed and will be published at a later date.

Supplementation. Supplementation of this regulation and establishment of command and local forms are prohibited unless prior approval is obtained from HQDA

(DASG-RDZ), 5109 Leesburg Pike, Falls Church, VA 22041-3258.

Interim changes. Interim changes to this regulation are not official unless they are authenticated by the Administrative Assistant to the Secretary of the Army. Users will destroy interim changes on their expiration date unless sooner superseded or rescinded.

Suggested Improvements. The proponent agency of this regulation is the Office of the Surgeon General. Users are invited to send comments and suggested improvements on DA Form 2028 (Recommended Changes to Publications and Blank Forms) directly to Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21701-5012. Users within the U.S. Army Health Services Command (HSC) will forward DA Form 2028 through Commander, U.S. Army Health Services Command, ATTN: HSHN-I, Fort Sam Houston, TX 78234-6060.

Distribution. Distribution of this publication is made in accordance with the requirements on DA Form 12-09-E, block number 3442, intended for command level D for Active Army. This publication is not distributed to ARNG and USAR.

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*This regulation supersedes AR 40-38, 15 April 1984.

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Glossary

Chapter 1 Introduction

1-1. Purpose

In recognition of the importance of organizing investigations where postgraduate education programs are conducted and for the advancement of medical science and its military and nonmilitary application to patient care, this regulation—

a. Sets policies, procedures, and responsibilities for the participation of human subjects and the accountability for material and funds used in CIPs.

b. Prescribes Army policy on the conduct and management of CIs including—

- (1) Command responsibilities.
- (2) Review process requirements.
- (3) Approval authorities.
- (4) Reporting requirements (RCS MED-300(R1)).

c. Allows a decentralized approval option for elements that have established review committees and an internal review process.

1-2. References

Required and related publications and prescribed and referenced forms are listed in appendix A.

1-3. Explanation of abbreviations and terms

Abbreviations and special terms used in this regulation are explained in the glossary.

1-4. Limitations of this regulation

a. CI is an essential component of optimum health care and consists of organized scientific inquiry into health care problems of significant concern to members of the Defense Eligibility Enrollment System (DEERS). Nothing in this regulation is intended to limit the authority of a health care practitioner to provide emergency medical care under the applicable law of the jurisdiction in which the care is provided.

b. Protocols for the use of drugs or Schedule I controlled substances for investigational purposes will be approved as per AR 40-7.

c. Investigations of medical equipment for use in other than fixed MTFs or DTFs are conducted under AR 70-10. In the conduct of such investigations, nothing in this regulation is intended to supersede requirements for health hazard or other safety reviews required by Department of the Army (DA) regulations.

d. The guidance in this regulation pertains to the following:

(1) CIs and behavioral studies involving human subjects, regardless of whether funding is provided through DA funds or by grant or gift.

(2) Clinical studies involving new drugs, biologicals, vaccines, or investigational medical devices.

(3) Clinical studies involving the deliberate exposure of human subjects to nuclear weapons effect, chemical warfare agents, or biological warfare agents.

(4) The administration and funding of the CIP.

e. The provisions of this regulation do not apply to epidemiological surveys that are of no more than minimal risk as set forth in the human protection regulations issued by the Department of Health and Human Services (DHHS). (See the DHHS entry in app A.) See appendix B for a listing of exempt studies.

Chapter 2 Responsibilities

2-1. Under Secretary of Defense for Acquisition

Under DODD 3216.2, the Under Secretary of Defense for Acquisition (USD(A)) or designee is the approval authority for studies involving the exposure of human subjects to nuclear weapons effect or to chemical or biological warfare agents.

2-2. Assistant Secretary of Defense (Health Affairs)

Under DODD 3216.2, the Assistant Secretary of Defense (Health Affairs) (ASD(HA)) serves as the Department of Defense (DOD) representative on matters relating to implementation of DHHS and Food and Drug Administration (FDA) regulatory requirements. (See the DHHS and FDA entries in app A.)

2-3. Deputy Chief of Staff for Personnel

The Deputy Chief of Staff for Personnel (DCSPER) will approve or disapprove those studies involving alcohol and drug abuse programs.

2-4. The Surgeon General

The Surgeon General (TSG) will—

a. Prepare policies and regulations on clinical investigations.

b. Establish and maintain the Human Subjects Research Review Board (HSRRB), which is chaired by the Assistant Surgeon General for Research and Development.

c. Establish and maintain the Human Use Review and Regulatory Affairs Office (HURRAO), to be attached to the U.S. Army Medical Research and Development Command (USAMRDC) and to report to the Assistant Surgeon General for Research and Development.

d. Approve or disapprove CI proposals from MTFs and DTFs from major Army commands (MACOMs) that do not have a human use committee (HUC) or an internal review process.

e. Provide an evaluation of protocols as described in paragraphs 2-1 and 2-3 of this regulation to the USD(A) and DCSPER.

f. Be the approval authority for studies and research protocols involving human subjects using Schedule I controlled drug substances.

g. Provide direct medical followup, when appropriate, on research subjects to ensure that long-range problems are detected and treated.

h. Report on a frequent basis, findings associated with classified investigational drug and device studies to the USD(A), the ASD(HA), and the FDA.

i. Be the approval authority for all in-house and contract research (other than that noted in paras 2-1, 2-3, 2-5, and 2-7) involving human subjects for which the Army has been designated the executive agent. Except for the categories of research for which TSG is specifically designated as the approval authority, TSG may delegate the authority to approve CIPs within the military chain of command to the lowest level operating a human subjects review process approved pursuant to paragraph 3-5.

2-5. Commander, Soldier Support Center—National Capital Region

Under AR 600-46, the Commander, Soldier Support Center—National Capital Region (SSC-NCR), is the approval authority for attitude and opinion surveys or Army occupational surveys.

2-6. Major Army commanders

When a CI is proposed, the MACOM commander will—

a. Promote, manage, and support the performance of CIs, recognizing the importance of organizing investigations where postgraduate education programs are conducted.

b. Ensure the effective implementation of the policies and procedures contained in this regulation.

c. Use the established review process through TSG's HSRRB for all protocols or establish a HUC and implement a review process consistent with the policies and procedures contained in this regulation.

d. Ensure that research volunteers are adequately informed concerning the risks associated with their participation, providing them with any newly acquired information that may affect their well-being as that information becomes available.

2-7. Commander, U.S. Army Health Services Command

The Commander, U.S. Army Health Services Command (HSC), will—

a. Comply with paragraph 2-6.

b. Establish and maintain within the U.S. Army Health Care Studies and Clinical Investigation Activity, the Clinical Investigation Program Division 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 CIP.

c. Ensure that commanders of Army medical centers (MED-CENs) within HSC—

- (1) Are responsible for all CIs conducted within the MEDCEN.
- (2) Organize a clinical investigation support system within a separate hospital organizational structure to implement the CIP.
- (3) Appoint a clinical investigation committee, a HUC, and an animal use committee (AUC).

d. Be the approval authority for—

- (1) Investigational drug studies except those involving Schedule I substances in humans.
- (2) Investigational medical devices studies involving humans.
- (3) CIs involving non-DA sponsored Notice of Claimed Investigational Exemption for a New Drug (IND) or Investigational Device Exemption (IDE).

2-8. Commanders of other major medical commands (overseas)

When a CI is proposed, the commander will comply with the applicable portions of paragraphs 2-6 and 2-7.

2-9. Commanders of medical and dental treatment facilities other than medical centers

a. Commanders of MTFs and DTFs assigned to the HSC should use their regional MEDCEN for CI support or seek approval from headquarters, HSC, to—

- (1) Organize, within their authorized and available resources, support for CIs.
- (2) Establish committees and the review process prescribed by this regulation, or refer proposals for committee review to the department of clinical investigation (DCI) at their regional supporting MEDCEN.

b. Commanders of MTFs and DTFs assigned to major medical commands (overseas) may, with MACOM approval—

- (1) Organize within their authorized and available resources, support for CIs.
- (2) Establish committees and the review process prescribed by this regulation or, for protocols proposing to use human subjects, refer the protocol to TSG's HSRRB.

2-10. HSRRB, HURRAO, and investigators

a. HSRRB members will—

- (1) Evaluate methods by which DA involves human subjects in CIs.
- (2) Recommend policy to TSG on the treatment of volunteers consistent with current moral, ethical, and legal standards.
- (3) Evaluate protocols submitted to TSG for approval.
- (4) Maintain documentation of approved protocols, to include continuing review for CIs conducted by MACOMs without an established internal review process.

b. The Chief, HURRAO will—

- (1) Provide, for TSG, administrative support for the HSRRB.
 - (2) Conduct a compliance review of all protocols submitted to TSG for approval.
 - (3) Submit DA-sponsored INDs and IDEs directly to the FDA.
 - (4) Submit DA-sponsored New Drug Applications (NDAs) directly to the FDA.
 - (5) Maintain DA record files for IND, IDE, and NDA submissions to the FDA.
 - (6) Conduct postmarketing surveillance for NDAs sponsored by DA.
 - (7) Serve as the DA point of contact for policies and regulations on human use in CIPs.
 - (8) Advise and assist MACOMs and DA staff agencies that conduct CIs using human volunteers.
- c. Investigators will—

(1) Prepare a protocol following the policies and procedures in this regulation.

(2) Prepare and maintain adequate records on—

(a) Receipt, storage, use, and disposition of all investigational drugs issued to the investigator by the pharmacy and investigational devices issued to the investigator by the activity responsible for storing them.

(b) Case histories that record all observations and other data important to the study.

(c) Volunteer informed consent documents (app C).

(3) Prepare progress reports, including annual reports (Clinical Investigation Program, RCS MED-300(R1)), as determined by the approving authority and regulatory agencies. (See app D for the annual report format.)

(4) Prepare and file an investigator sponsored IND or IDE as appropriate.

(5) Promptly notify the approving official through the medical monitor and the HUC of adverse effects caused by the CI.

(6) Report serious and unexpected adverse experiences involving the use of investigational drugs or devices to the sponsor or the FDA in accordance with AR 40-7.

(7) Ensure that the CI has been approved by the proper review committee(s) before starting, changing, or extending the investigation (see paras 3-5 b (1) through (6)).

(8) Ensure that all subjects or their representatives, including subjects used as controls, are fully informed of the nature of the investigation to include potential risks to the subject.

(9) Ensure that investigational drugs or devices are administered only to subjects under the investigator's personal supervision or that of a previously approved associate investigator.

(10) Ensure that a new principal investigator (PI) is appointed if the PI cannot complete the CI for reasons such as permanent change of station (PCS) or retirement.

(11) Apprise the HUC of any investigator's noncompliance with the CI protocol.

(12) Seek HUC approval for other investigators to participate in the CI.

(13) Ensure that studies involving attitude or opinion surveys are approved in accordance with AR 600-46. (See para 3-5 b (6).)

d. The medical monitor will be responsible for serving as an advocate for the medical safety of the volunteers. The monitor will have other responsibilities as determined by the approving official and will have the authority to terminate an individual volunteer's participation in the study or suspend the study for review by the HUC.

Chapter 3 Clinical Investigation or Research

3-1. CI principles

a. CI is an essential component of medical care and teaching that is intended to achieve the following:

- (1) Improve the quality of patient care.
- (2) Generate an atmosphere of inquiry responsive to the dynamic nature of health sciences.
- (3) Promote high professional standing and accreditation of health and graduate medical education programs.

b. Military contingency requirements take precedence over the requirements of the CIP.

c. User testing, as defined in AR 15-38 or AR 71-3, will not be conducted under a CI protocol when the CI is greater than minimal risk.

3-2. Use of animals in CIs

CI proposals involving animals will be conducted in accordance with AR 70-18/SECNAVINST 3900.38/AFR 169-2/DARPAINST 18/DAINST 3216.1/USUHSINST 3203.

3-3. Use of humans in CIs

a. Only persons who are fully informed and volunteer in advance to take part may be used as subjects in CIs except when the measures used are intended to be beneficial to the subject, and informed consent is obtained in advance from a legal representative on the subject's behalf. (See app E.)

b. Any human tissue or bodily fluid obtained by autopsy that is used in a CI will be donated by the next of kin or legal representative of the person from whom the tissue or fluid is removed. Donation is made by written consent and the donor relinquishes ownership and rights to the tissue or fluid. Consent to donate does not rule out payment for such donation.

c. Any human tissue or bodily fluid linked by identifiers to a particular person obtained by surgical or diagnostic procedures and intended for use in CIs will be donated by the person from whom the tissue or fluid is removed or, in the event of death or legal disability of that person, the next of kin or legal representative of such person. Donation is made by written consent and the donor relinquishes ownership and rights to the tissue or fluid. Consent to donate does not rule out payment for such donation.

d. The determination of the level of risk in a CI protocol is made by a HUC established in accordance with this regulation.

e. Moral, ethical, and legal concepts on the use of human subjects will be followed as outlined in this regulation. Voluntary consent of the human subject is essential. Military personnel are not subject to punishment under the Uniform Code of Military Justice (UCMJ) for choosing not to take part as human subjects (Manual For Courts-Martial (MCM 1984)). Further, no administrative sanctions will be taken against military or civilian personnel for choosing not to participate as human subjects.

f. CIs using human subjects are conducted in such a manner that risks to the subjects are minimized and are reasonable in relation to anticipated benefits.

g. The proposed number of subjects will be the minimum needed to ensure a statistically valid conclusion.

h. The CI is conducted so as to avoid unnecessary physical and mental suffering. Preparations will be made and adequate facilities provided to protect the subject and investigators against all foreseeable injuries, disabilities, or death. Such research is not conducted if there is reason to believe that death or injury will result.

i. Volunteers must be given adequate time to review and understand all information before agreeing to take part in a study.

j. Volunteers are authorized all necessary medical care for injury or disease that is a proximate result of their participation in clinical research. (See app E.)

(1) Medical care for DEERS-eligible civilian employees who volunteer and who perform duty as volunteers during their regularly scheduled tours of duty will be provided care in accordance with AR 40-3.

(2) Medical care costs and subsistence charges for all other categories of personnel who are routinely authorized care in a military MTF under AR 40-3 will be waived while the volunteer is in the hospital if the volunteer would not normally enter the hospital for treatment but is requested to do so to facilitate the CI. This also applies to the volunteer's extension of time in a hospital for a CI when the volunteer is already in the hospital. The costs for subsistence charges do not apply for CI or research volunteers in accordance with AR 40-3, paragraph 4-60. For those facilities on the Automatic Quality of Care Evaluation Support System (AQCESS), the patients will be coded as patient category X-75.

k. Information obtained by the DOD during or as a result of an epidemiologic-assessment interview with a human immunodeficiency virus (HIV) seropositive soldier may not be used to support adverse personnel action against the soldier (see chap 6, AR 600-110).

l. The use of prisoners of war and detainees as human research subjects is prohibited.

m. Minors may be enrolled as experimental subjects in clinical studies when the following conditions are met:

(1) The risk is justified by the intended benefit to the minor.

(2) The intended benefits are at least as favorable to the minor as those presented by available alternatives.

(3) A legally authorized representative has authorized, in advance, for the minor to participate in the clinical study.

(4) The minor, if capable, has assented in writing. In determining whether the minor is capable of assenting, the HUC will consider the minor's age, maturity, and psychological state, as well as any applicable State and local law concerning the minor's legal capacity to assent. The HUC may waive assent for some or all minors involved in the study if it determines that the capability of some or all of the minors is so limited that they cannot be reasonably consulted or the procedure involved in the study holds out a prospect for direct benefit that is important to the health or well-being of the minor and is available only in the context of the study.

n. Only persons judged qualified by the appropriate approving official will conduct research involving human subjects.

o. A medical monitor who is not involved as an investigator in the protocol will be appointed if the HUC or approving official determines that the risk is more than minimal. A medical monitor may be appointed to minimal risk studies if so determined by the HUC or approving authority.

p. Safeguards or special conditions imposed on a protocol by a HUC may not be reduced or waived by the approving official upon approval of the protocol. The approving official may require additional safeguards, disapprove the protocol, or refer it to a higher review and approving authority.

q. Clinical studies on medical devices will be conducted in accordance with part 812, title 21, Code of Federal Regulations (21 CFR 812). (See the FDA entry in app A.)

r. Drugs, placebos, biologicals, and vaccines not commercially available (that is, investigational drugs) will be received, stored, and controlled by the pharmacy and will not be dispensed without an approved protocol.

s. All investigational medical devices and medical devices not commercially available are received, stored, and controlled in a manner as determined by the MTF or DTF commander and are not issued without an approved protocol.

3-4. Conducting CIPs

MACOM commanders conducting a CIP will—

a. Publish directives and regulations for—

(1) Establishing an internal review process to include a clinical investigation committee; a HUC, if applicable; and an AUC, if applicable.

(2) Protocol preparation.

(3) The use of animals in CIs.

(4) The use of human subjects in CIs.

(5) Funding and administration of the CIP.

b. Establish a system that will permit the identification of volunteers who have participated in clinical studies involving investigational drugs or devices. Such a system will be established in accordance with AR 340-21 (see para 3-5 h for a discussion of "duty to warn").

c. Forward one copy of the regulations and directives and subsequent changes to these publications through the MACOM commander to the Assistant Surgeon General for Research and Development, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21701-5012, within 60 days of publication.

3-5. Conducting CIPs involving humans

a. *Establishing a HUC.* As noted in paragraphs 2-6 c and 2-9 a and b, commanders of MTFs and DTFs will either implement their own HUC or use their regional MEDCEN DCI or TSG's HSRRB.

(1) HUCs will be established for CIs in accordance with appendix F.

(2) MTFs and DTFs assigned to HSC that are seeking initial approval of an internal review process will forward the items listed in (a) and (b) through command channels to Commander, U.S. Army Health Services Command, Health Care Studies and Clinical

Investigation Activity, ATTN: HSHN-I, Fort Sam Houston, TX 78234-6000.

(a) One copy of implementing directives and regulations describing protocol preparation and policies for CIs involving human subjects.

(b) A listing of the membership of the HUC and the curriculum vitae for each member.

(3) MEDCENs, MTFs, and DTFs assigned to major medical commands (overseas) that are seeking initial approval of an internal review process will forward the items listed in (2)(a) and (b) above through command channels to the Assistant Surgeon General for Research and Development, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21701-5012.

(4) CIs involving human subjects may not commence until the implementing directives and HUC membership have been approved by HQ, HSC, for all units assigned to that Command or TSG for all other units.

b. Protocol and/or plan review before submission to a HUC.

(1) If a study calls for the use of volunteers (either as the direct or indirect object of the study), a protocol is prepared. Certain studies may be exempt (see app B). The format at appendix G should be followed but may be modified to meet local requirements. Informed consent will be documented using DA Form 5303-R (Volunteer Agreement Affidavit) in accordance with appendix C (see 3-5 c). DA Form 5303-R will be reproduced locally on 8½- by 11-inch paper. A copy for reproduction is located at the back of this regulation.

(2) If a study calls for the use of tissue or fluids obtained from a human, and is not an exempt study as defined by paragraph B-6, a protocol is prepared. (The informed consent document used in these cases may be the DA Form 5303-R or an overprinted consent for surgery or autopsy.) The following must be considered in determining whether an informed consent is required:

(a) Fluid or tissue obtained at autopsy—informed consent is required.

(b) Fluid or tissue obtained at surgery or as the result of a diagnostic procedure and linked by identifiers directly or indirectly to a particular person intended for CI—informed consent is required.

(c) Fluid or tissue obtained at surgery or as the result of a diagnostic procedure not intended for a CI and not linked by identifiers directly or indirectly to a particular person—no informed consent is required.

(d) Fluid or tissue obtained from a tissue or blood bank that is linked to a personal identifier and the research data are recorded in such a manner as to identify the donor—informed consent is required.

(e) Fluid or tissue obtained from a tissue or blood bank that is linked to a personal identifier, but the research data are recorded in such a manner that the donor's identity is unknown—no informed consent is required.

(f) Fluid or tissue obtained from a tissue or blood bank that is not linked to a personal identifier—no informed consent required.

(3) The protocol will be submitted to the clinical investigation committee composed of individuals qualified by training and experience and appointed by the commander of the unit to evaluate the validity of the protocol. The purpose of this peer review is to assure that the protocol design will yield scientifically useful data that meet the objective(s) of the study. The committee recommendations and actions taken by the investigator in response to the recommendations will be submitted with the protocol to the HUC.

(4) When applicable, the protocol is submitted to the radiation control committee (RCC), or equivalent, established in accordance with TB MED 525. Exposure of human research subjects to ionizing radiation not intended for diagnosis or treatment but as a direct result of their participation in a CI requires that the local institutional review board (IRB) determine the risk to benefit to ensure that potential subjects can be appropriately informed before deciding

to participate. Radiation exposure as the result of diagnosis or treatment must be documented as such in the protocol, and RCC review is not required. All other CI protocols that indicate exposure of human subjects to ionizing radiation will contain RCC risk assessments prior to IRB review. All protocols (human or animal) involving the use of radioactive material should be forwarded to the local Radiation Protection Office to determine if further RCC review is required.

(5) The radioactive drug research committee, in accordance with 21 CFR 361 (see the FDA entry in app A), may recommend approval of certain radioactive drugs for use in human research subjects that otherwise might require an IND or an approved NDA. The radioactive drug may be used to obtain basic information regarding human physiology, pathophysiology, or biochemistry but may not be used for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans. The investigator will also obtain RCC review.

(6) If the study calls for the use of an attitude or opinion survey, as defined in AR 600-46, it may not be considered a CI. If such studies are planned, the SSC—NCR must be contacted by the investigator to determine whether the survey requires the clearance of that center. This information should accompany the proposal when it is submitted to the DCI for review. Surveys that cross over command lines or are sent to other services require SSC—NCR clearance, but surveys within a unit conducted by that unit do not. For example, surveys conducted on inpatients, soldiers assigned to the unit, and family members of soldiers assigned to the MTF or DTF do not require clearance. Surveys of outpatients that can be accomplished in the clinic and do not require the patients to take them home do not require clearance. Inquiries should be directed to Commander, Soldier Support Center—National Capital Region, Attitude and Opinion Survey Division, ATTN: ATNC-MOA, 200 Stovall Street, Alexandria, VA 22332-0400 (AUTOVON 221-9680). The Center serves as a reference facility on the preparation of surveys. Investigators should coordinate with the SSC—NCR to determine if similar surveys have been conducted. When required, the clearance of the SSC—NCR will accompany protocols when they are submitted for IRB review.

c. Informed consent documentation.

(1) Informed consent generally pertains to the agreement to participate in the protocol before such participation begins. Informed consent also applies, however, after the study begins when informed consent for further participation is required because information that might have affected the volunteer's willingness to have originally agreed to participate in the study or to continue to participate in the study comes to the attention of the investigator or HUC.

(2) A written informed consent documents the act of consent. The purpose of an informed consent document is to provide the volunteer with sufficient information to make a reasonable decision regarding whether to participate in the study and to provide evidence that consent was obtained. Whether the information is provided orally or in writing, the information pertinent to the decision to participate in the study must be in writing. If information material to the volunteer's decision to participate in the study is discovered after the volunteer consents to participate in the study, the volunteer must be informed of the new information and a new informed consent, with appropriate written documentation, must be obtained from the volunteer. Consent procedures must conform to Federal, State, and local law.

(3) The volunteer's agreement to participate in the protocol will be documented using DA Form 5303-R in accordance with appendix C. The volunteer agreement will be written in language that is easily understandable by the subject. Exculpatory language should not be used in informed consent documents. An *English* translation of the form will be provided to the HUC if the form is completed in a language other than English. Where necessary, an addendum to the DA Form 5303-R may be used when, in the determination of the PI and the HUC, additional space is needed to fully explain aspects of the research.

d. HUC actions on protocol review after submission to a local HUC. The HUC will—

(1) Determine the level of risk associated with the protocol: minimal risk or more than minimal risk.

(2) Make the following recommendations to the approving authority: Approved, approved with modification, defer review to higher authority, disapproved, or exempt from further human use review.

(3) Determine the adequacy of the proposed consent process, as well as the information to be presented to the subject. The HUC should evaluate all elements of informed consent in accordance with the applicable portions of appendix C. The committee may require that information, in addition to that specifically mentioned in appendix C, be given to the subject when the HUC determines that the information would meaningfully add to the protection of the rights and welfare of the subject. The committee may waive the requirement for a signed informed consent for some or all of the subjects if it finds that either—

(a) The only record linking the subject and the protocol would be the consent document, and the principal risk is potential harm from breach of confidentiality. Each subject will be asked whether the subject wants documentation linking the subject with the protocol, and the subject's wishes will govern.

(b) The CI presents no more than minimal risk of harm to subjects and does not involve procedures for which written consent is normally required outside of the research context. In cases where the documentation requirement is waived, the HUC may require the investigator to provide subjects with a written statement regarding the protocol. Waiver of the requirement for a signed consent form does not waive the requirement for informed consent consistent with 10 USC 980 and DODD 3216.2.

(4) Review protocols involving minors as experimental subjects. The committee will determine if assent is required. If required, DA Form 5303-R will be used for documentation of assent. The HUC may waive the requirement for assent for minors consistent with the standards required by 45 CFR 46.408. (See the DHHS entry in app A.) However, a determination that the assent requirement may be waived does not affect the requirement to obtain the consent of the minor's legal representative.

(5) Conduct a continuing review of the protocols approved by the HUC at intervals appropriate to the level of risk, but at least annually. The format for the review (for example, progress report from the investigator) will be determined by the HUC.

(6) Review protocols involving medical devices. HUCs reviewing CIs of medical devices may also have to determine whether the device presents a significant or nonsignificant risk. The determination that a device presents a nonsignificant or significant risk is initially made by the sponsor. The HUC may ask for and obtain certain information prior to determining the risk status of the device. A risk assessment determination and the rationale of the sponsor's decision should be provided by the sponsor. The HUC may ask the sponsor whether other HUCs have reviewed the proposed study and what determination was made. The sponsor should notify the HUC of the FDA's assessment of the device's risk if such an assessment has been made. The HUC may also consult the FDA for its opinion. In deciding if a device presents significant or nonsignificant risks, the HUC should consider the device's total risks, not those as compared with the risks of alternative devices or procedures. If the device is used in conjunction with a procedure involving risk, the HUC should consider the risks of the procedure in conjunction with the risks of the device. The HUC may choose to agree or disagree with the sponsor's initial determination of degree of risk. Sponsors must notify FDA when a HUC determines that a device, judged by the sponsor *not* to present a significant risk, should be categorized as a significant risk device. On rare occasions, FDA may come to a different conclusion than that reached by the HUC, and FDA may overrule a HUC's decision that a device presents a nonsignificant risk. Once a decision on the degree of risk is reached, the HUC should consider whether the study should be approved or not. Some studies involving nonsignificant risk devices may also be considered minimal risk studies and thus may be reviewed through the expedited review procedure established by the HUC. The FDA considers

studies of all significant risk devices to present more than minimal risk; thus, full HUC review for all studies involving significant risk devices is necessary. In considering whether a study should be approved, the HUC should use the same criteria it would use in considering approval of any research involving an FDA regulated product. In considering the risks of the device as they pertain to HUC approval (as opposed to whether or not FDA should approve the IDE), the HUC should not simply judge the increase in risk over standard treatment but rather the risk of the procedure as a whole. The risks and benefits of a medical device compared to the risks and benefits of alternative devices or procedures should be considered by the HUC in deciding the approvability of a study involving a medical device. CIs of intraocular lenses also require review and approval of a HUC established in conformance with this regulation.

Note. Certain categories of research may be reviewed by the HUC using the expedited review procedures 3-5 g below. Exempt categories of research are listed in appendix B.

e. Actions of approving official on protocol review. The approving official—

(1) May accept or reject the recommendations of the HUC.

(2) Will not approve a CI that is disapproved by the HUC.

(3) Will appoint a medical monitor (see glossary) to studies that are greater than minimal risk and, if deemed appropriate, for those studies that are minimal risk.

(4) May require additional safeguards, may disapprove the protocol, or may refer it to a higher review committee and approving authority; however, safeguards or special restrictions imposed on a protocol by a HUC may not be reduced or waived by the approving official upon approval of the protocol.

(5) Will obtain a health hazard assessment prior to approving a research protocol involving human subjects in the operation of military materiel (see AR 40-10).

(6) Will notify the investigator of the decision to approve or disapprove the CI proposal or of modifications required to secure approval.

(7) Will ensure the continued evaluation of CI programs to assure that the policies and procedures established by this regulation are being followed.

(8) Will, when higher approval authority is required, send two copies of the protocol, informed consent documentation (DA Form 5303-R), all minutes of committees reviewing the protocol, and the commander's recommendations through command channels to the appropriate headquarters. CIs requiring TSG or higher level approval will be forwarded to the Assistant Surgeon General for Research and Development, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21701-5012.

f. Actions of organizations without a local HUC.

(1) The investigator will accomplish the actions noted in 3-5 *b* and *c* above.

(2) The commander will accomplish the actions noted in 3-5 *e* (5) through (7) above and forward the protocol with his or her recommendations through the chain of command to the next level of command having an approved HUC.

g. Expedited review procedures. These procedures will be as follows:

(1) CIs involving no more than minimal risk and in which the only involvement of human subjects will be in one or more of the categories listed in appendix H may be reviewed by the HUC through the expedited review procedure.

(2) The HUC may also use the expedited review procedure to review minor changes in previously approved protocols during the period for which approval is authorized. Under an expedited review procedure, the HUC chairman or one or more HUC reviewers designated by the chairman may carry out the review. The reviewers may exercise all of the authorities of the HUC except disapproval. Protocols may be disapproved only after review according to the nonexpedited procedure in 3-5 *d* above.

(3) Each HUC using an expedited review procedure will adopt a

method for keeping all members and the commander advised of approved proposals.

(4) The approving official may restrict, suspend, or end a HUC's use of the expedited review procedure when necessary to protect the rights or welfare of subjects.

h. Duty to warn. Commanders must ensure that volunteers are adequately informed concerning the risks involved with their participation in the study and provide volunteers with newly acquired information that may affect their well-being. The "duty to warn" exists even after a volunteer has completed participation in the study. To accomplish this, the MTF or DTF conducting the study will follow the procedures established by the MACOM to permit the identification of volunteers who have participated in clinical studies conducted by that command. The "duty to warn" also extends to others whose health may be affected by a volunteer's participation. (See para 3-4 *b.*)

i. Determining responsibility for review of protocols when more than one DOD or DA component is involved. When more than one DOD or DA component is involved in a study, the commander will determine primary responsibility based upon consideration of whether the subjects are inpatients or outpatients of a DOD MTF, whether the study is conducted in-house or by contract, or whether the prospective human subjects are members of a DOD component.

(1) When the study, regardless of in-house or contract status, involves use of patients in a DOD MTF, the component to which the MTF belongs organizationally has primary responsibility except as provided in (3) below.

(2) For CIs not involving the use of inpatients at a DOD MTF, primary responsibility rests as follows:

(a) If the study is done on grant or contract, primary responsibility rests with the component providing funds.

(b) If the study is conducted in-house, primary responsibility rests with the component to which the PI is assigned.

(c) If the study is not funded by a DOD or DA component and there is no DOD or DA PI, primary responsibility rests with the component to which the prospective human subject is assigned.

(3) Studies funded by the Uniformed Services University of the Health Sciences (USUHS) or the Director, Defense Nuclear Agency, will be reviewed and approved in accordance with policies established by the funding agency and DODD 3216.2.

j. Records. The department or service that has the responsibility for providing CI support in activities conducting CIs involving volunteers will maintain records in accordance with AR 25-400-2. These records are pertinent to each CI conducted and will include, at a minimum—

(1) Documentation of approval to conduct the study.

(2) A copy of the approved protocol.

(3) The volunteer's signed informed consent (DA Form 5303-R).

(4) Case report forms for drug or device studies.

(5) A summary of the results of the CI, to include any untoward reactions or occurrences.

k. Technical reports and publications.

(1) Technical reports are required for studies funded by the RDTE Major Defense Program 6 Fund (see AR 37-100-FY), will be prepared in accordance with AR 70-31, and follow the format established in ANSI-STD-Z39.18-1987 or its revisions.

(2) Publications regarding the results of CIs will be released by the approving official in accordance with the provisions of AR 360-5 and AR 70-14 and will contain this statement: "The investigators have adhered to the policies for protection of human subjects as prescribed in 45 CFR 46." (See the DHHS entry in app A.)

(3) Publications regarding the results of CIs conducted by contract or grant will note adherence with 45 CFR 46, as amended. (See the DHHS entry in app A.)

3-6. Funding and administration of CIPs

a. Funding.

(1) CIPs will be funded with procurement funds and with operating funds from Major Defense Program 8 (see AR 37-100-FY; FY denotes the fiscal year contained in the publication number).

(2) CIs on health problems encountered in active duty military personnel may be funded from Major Defense Program 6 operating funds (see AR 37-100-FY). The decision to fund such investigations will be made on a case-by-case basis by the Commander, USAMRDC. Such investigations must be related to—

(a) USAMRDC's designated research areas.

(b) One or more line items comprising USAMRDC's available RDTE appropriation.

(3) CIs may be conducted with funds obtained by grant from another Federal agency.

(4) CIs may be conducted with funds obtained by grant from corporations, foundations, funds, or educational institutions operated primarily for scientific, literary, or educational purposes that are tax-exempt under the provisions of 26 USC 501.

(5) Gifts may be used to provide funds for CIs under AR 1-100.

(6) Army health care personnel are prohibited from accepting any compensation in addition to their normal pay and allowances for performing duties within the scope of the CIP.

(7) In conducting CIs, there may be no competition with available commercial facilities in providing services to entities outside the Federal Government.

(8) CIs will not be conducted with funds or other resources provided by business groups operating for profit, foreign governments, and political organizations; however, investigational drugs, devices, biologics, vaccines, or placebos may be used in approved CI protocols where an audit trail and proper accounting have been established as determined by the MTF or DTF commander.

b. Administration of CIs and grants.

(1) Monetary grants or gifts received for CIP will be administered by an officer, normally the comptroller, designated by the MTF or DTF commander. Nonmonetary grants or gifts received for CIP will be administered by an officer designated by the MTF or DTF commander. This officer must be someone other than the PI or anyone directly involved in the conduct of the study. Disbursements to the MTF or DTF from cooperative grants held by non-DOD institutions must be administered by a designated officer not directly involved with the conduct of the study.

(2) Investigation objectives should allow for the conclusion of a study within the tour of duty of the investigator. If this is not possible, plans should be made by the investigator to permit continuation of the study when that investigator leaves.

(3) The initiation of a protocol request by the investigator to support a clinical study is the means of obtaining funds. For intramurally funded studies, the format and mechanism will be established by the MACOM. For extramurally funded studies, the format and mechanism will be established by the MACOM in consonance with the procedures required by the funding institution. In addition to Major Defense Program 8 funds (see AR 37-100-FY) appropriated to conduct clinical studies, the following sources may be used:

(a) *USAMRDC.* The USAMRDC may provide Major Defense Program 6 funds (see AR 37-100-FY) to MTFs and DTFs to support clinical studies related to USAMRDC's designated research areas and one or more line items comprising USAMRDC's available RDTE appropriation. The Broad Agency Announcement (BAA), published by the USAMRDC, addresses areas of research interest in that Command and the format to be followed when submitting a proposal. Funds may be provided to facilities on a noncompetitive basis (that is, not in competition with the private sector). Proposals should be submitted through the MACOM to Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-ACQ, Fort Detrick, Frederick, MD 21701-5012. Copies of the BAA can be obtained from the Commander, USAMRDC.

(b) *USUHS.* Individuals who possess faculty appointments to the USUHS may apply for grant funding. The proposal should be submitted through the MACOM and subsequently through the USUHS department head (for example, an adjunct professor of ophthalmology would submit the proposal through the Chairman, Department of Surgery) to the Director, Grants Management, USUHS, 4301 Jones Bridge Road, Bethesda, MD 20814-4799. These grants are limited and are awarded on a very competitive basis. For additional information, contact the Director, Grants Management, USUHS.

(c) *Henry M. Jackson Foundation for the Advancement of Military Medicine.* Individuals who possess faculty appointments to the USUHS as adjunct assistant professor and higher may apply for grant funding. The proposal should be submitted through the MACOM and subsequently through the USUHS department head to the Director, Grants Management, USUHS, who will forward the proposal to the Foundation. These grants are managed by the Foundation, not USUHS. For additional information, contact the Director, Grants Management, USUHS.

(d) *National Institutes of Health (NIH).* Any PI may apply for grant funds from the NIH. It is NIH policy that any grant to another Federal agency must first be approved by the Service Secretary. Proposals are submitted through command channels to OTSG, ATTN: SGPS-RMB, 5109 Leesburg Pike, Falls Church, VA 22041-3258.

(e) *Corporations, foundations, funds, or educational institutions organized and operated primarily for scientific, literary, or educational purposes.* AR 621-7 authorizes investigators to apply for grants from nongovernment activities. Applications will follow the procedures outlined in AR 621-7.

(f) *Cooperative oncology groups.* These groups receive grant moneys from the National Cancer Institute (NCI), NIH, to support studies of investigational oncologic agents. Funds are provided based on the number of patients enrolled in a study. DA clinical investigators who conduct cooperative studies with an oncology group(s) may draw the funds allocated to the group by NCI for patients being treated and studies by the Army investigator in an MTF or DTF. In this case, the oncology group is functioning as an agent of the Federal Government—that is, NCI—in granting these funds to the CIP.

(g) *Gifts provided for CI study.* The donation of a gift for CI is accounted for in accordance with the guidelines established in AR 1-100. Drugs, placebos, biologics, vaccines, and medical devices that are not commercially available (see 21 CFR 312) under subchapter D of the FDA entry in appendix A and equipment loaned for use in the performance of an approved CI protocol with an audit trail and appropriate control mechanisms are not considered gifts. They will be receipted and accounted for as determined by the MTF or DTF commander.

(4) Any gift or grant funds used to support travel will not be disbursed in excess of Government per diem rates.

(5) Any gift funds not expended will be reprogrammed.

(6) Any grant funds not expended in the CI study will be refunded to the grantor by the facility or reprogrammed at the direction of the grantor.

(7) For grants, a document is signed by the commander of the MTF or DTF and a representative of the grantor specifying the nature of the grant including monetary value, requests of the grantor, and the conditions under which the facility accepts the grant, as well as a statement that the investigation is subject to delay or termination if required in the interest of the military mission.

(8) For gifts, a document is signed by the commander of the MTF or DTF and forwarded to the donor, specifying the nature of the gift including monetary value, requests of the donor, and the conditions under which the facility accepts the gift, as well as a statement that the study is subject to delay or termination if required in the interest of the military mission.

(9) Active duty military personnel may participate in clinical investigations as human subjects but will not be compensated for participation except when blood is furnished for—

(a) Transfusion into the veins of a person entitled to and undergoing treatment at Government expense, whether in a Federal hospital or institution or in a civilian hospital or institution.

(b) Blood banks or for other scientific and research purposes in connection with care of any person entitled to treatment at Government expense. The volunteer will be entitled such reasonable sum, not to exceed \$50, for each blood withdrawal as determined by the approving official. This fee may be paid provided that no payment is made to any person for blood withdrawal for the benefit of the person from whom it is withdrawn (24 USC 30).

(10) Retired military personnel may participate as human subjects in CIs. Such personnel may be compensated on a fee basis pursuant to a contract; however, if studies exceed 30 days their retired pay is subject to recomputation.

(11) Dependents and others entitled to medical care in MTFs or DTFs may participate as human subjects in CIs. These persons may be compensated on a fee basis pursuant to a contract.

(12) It is Government policy not to accept voluntary services from private citizens when the services may provide a basis for a future claim against the Government for their value. Therefore, such services will be accompanied by a statement signifying that the individual acknowledges that he or she will not be entitled to any compensation or future claim for these services. Private citizens may enter into an independent contractor relationship and participate for a fee in accordance with the procedure endorsed by the Comptroller General. (Volume 45, Decision of the Comptroller General, 1966, p. 649 (45 DCG 649 (1966)).)

(13) If a soldier, dependent, or other individual entitled to medical care and enrolled as a human subject loses his or her eligibility for care (for example, a sponsor separates from service prior to retirement), take the following action—

(a) Determine if the subject's continued participation is essential to his or her well-being (for example, participation in an oncology group protocol).

(b) Attempt to transfer the subject to a nonmilitary sponsored study in the community.

(c) Apply for Secretary of the Army designee status for the subject if transfer to a community based program cannot be accomplished prior to loss of eligibility. The termination of a subject's participation in a study that affects the subject's well-being without providing appropriate alternative care is not the policy of the DA.

(14) When DOD civilian employees volunteer to provide service within the scope of their employment, any duty performed during the employees regularly scheduled duty day will be considered constructive duty for which straight-time rates apply. Employees must have the approval of their immediate supervisor to participate during duty time. Participation outside the employee's scheduled duty, as during leave, is considered voluntary overtime for which payment or compensatory time must be granted as mandated by the Fair Labor Standards Act. These limitations on the provision of volunteer services by civilian employees are documented and signed by the employee and his or her supervisor prior to participating in the CI study. Accordingly, if an employee desires to participate as a volunteer in a study and the employee's supervisor concurs, the employee's participation is considered within the scope of employment. However, the employee will be compensated for participation as noted above and will not receive compensation from other sources.

(15) Individuals who enter the hospital or have their hospitalization extended due to participation in a CI will be coded as AQCESS patient category X-75.

(16) Active duty soldiers participating in studies whose purpose is to evaluate rations are not charged for the investigational or test item and do not forfeit their basic allowance for subsistence.

(17) Reprints of articles based on approved CI projects are official material as defined in AR 70-14. Purchase of such reprints will be made from Operations and Maintenance, Army funds.

(18) Commanders will ensure that all individuals participating in CI studies are apprised of their responsibilities and obligations regarding the legal and ethical aspects of such studies.

(19) DA Form 5303-R will be used to document informed consent. The investigator retains the original signed copy. A copy is provided to the volunteer. The investigator provides a copy of the signed form to the medical records custodian for inclusion in the volunteer's medical treatment record, if the volunteer agrees to its inclusion in the record.

(20) It is the "norm" in the community to use "leftover or excess" blood drawn for diagnostic procedures or expired blood donated to blood banks for CIs. This practice is based on the contention that the blood has been abandoned by the donor; however, the investigator must take into account that the patient or donor

has an absolute property right to the blood. Paragraph 3-3 *b* specifically prohibits the use of tissue or fluid obtained at autopsy from being used for clinical studies without the consent of the donor or next of kin. Paragraph 3-3 *c* specifically prohibits the use of tissue and fluid linked by an identifier and obtained by surgery or diagnostic procedure from being used for clinical studies without consent of the donor or next of kin, if the sample was obtained expressly for the purpose of doing a CI. Studies of tissue may be exempt from review by a HUC and informed consent to use such specimens may be waived by a HUC (see para 3-5 *b* (2)).

(21) Requests for exception to policy as stated in this regulation will be submitted to the Assistant Surgeon General for Research and Development, c/o Commander, U.S. Army Medical Research and Development Command, ATTN: SGRD-HR, Fort Detrick, Frederick, MD 21701-5012. Requests will then be submitted to TSG's HSRRB for evaluation and recommendations to TSG and TSG's recommendation to the USD(A) or ASD(HA), as appropriate.

Appendix A References

Section I Required Publications

ANSI-STD-Z39-18-1987

Scientific and Technical Reports: Organization, Preparation and Production. (Cited in para 3-5 *k* (1).) (This publication may be obtained from the Naval Publications and Forms Center, 5801 Tabor Avenue, Philadelphia, PA 19120-5099.)

AR 1-100

Gifts and Donations. (Cited in paras 3-6 *a* (5) and 3-6 *b*(3)(g)).

AR 15-38

Test Schedule and Review Committee. (Cited in para 3-1 *c* .)

AR 25-400-2

The Modern Army Recordkeeping System (MARKS). (Cited in paras 3-5 *j* and F-7 *b* .)

AR 37-100-FY (vols 1 and 2)

The Army Management Structure (AMS). (Cited in paras 3-5 *k*(1), 3-6 *a* (1) and (2), 3-6 *b* (3) and (3)(a), E-3, E-5, and the glossary.)

AR 40-3

Medical, Dental, and Veterinary Care. (Cited in para 3-3 *j* (1) and (2).)

AR 40-7

Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances. (Cited in paras 1-4 *b* and 2-10 *c*(6) and the glossary.)

AR 40-10

Health Hazard Assessment Program in Support of the Army Materiel Acquisition Decision Process. (Cited in para 3-5 *e* (5).)

AR 70-14

Publication and Reprints of Articles in Professional Journals. (Cited in para 3-5 *k*(2) and 3-6 *b* (17).)

AR 70-18/SECNAVINST 3900.38/AFR 169-2/DARPAINST 18/DNAINST 3216.1/USUHSINST 3203

The Use of Animals in DOD Programs. (Cited in para 3-2.)

AR 70-25

Use of Volunteers as Subjects of Research. (Cited in paras E-3 and E-5.)

AR 70-31

Standards for Technical Reporting. (Cited in para 3-5 *k* (1).)

AR 71-3

User Testing. (Cited in para 3-1 *c* .)

AR 335-15

Management Information Control System. (Cited in app G.)

AR 340-21

The Army Privacy Program. (Cited in para 3-4 *b* .)

AR 360-5

Army Public Affairs, Public Information. (Cited in para 3-5 *k* (2).)

AR 600-46

Attitude and Opinion Survey Program. (Cited in paras 2-5, 2-10 *c*(13), and 3-5 *b* (6).)

AR 600-110

Identification, Surveillance, and Administration of Personnel Infected with Human Immunodeficiency Virus (HIV). (Cited in para 3-3 *k* .)

AR 621-7

Acceptance of Fellowships, Scholarships, or Grants. (Cited in para 3-6 *b*(3) (*e*) .)

DHHS Regulation

Protection of Human Subjects (45 CFR 46). (Cited in paras 1-4 *e* , 2-2, and 3-5 *d* (4) and *k*(2) and (3).) (This publication may be obtained from the Department of Health and Human Services, Public Health Service, 200 C Street, Washington, DC 20204.)

FDA Regulation

Food and Drugs (21 CFR subchaps A, D, H). (Cited in paras 2-2, 3-3 *q*, 3-5 *b* (5), and the glossary.) (This publication may be obtained from the Department of Health and Human Services, Public Health Service, Food and Drug Administration, 200 C Street, Washington, DC 20204.)

TB MED 525

Control of Hazards to Health From Ionizing Radiation Used by the Army Medical Department. (Cited in para 3-5 *b* (4).)

Section II Required Publications

A related publication is merely a source of additional information. The user does not have to read it to understand this regulation.

AR 11-2

Internal Control Systems.

AR 40-66

Medical Record and Quality Assurance Administration.

AR 70-10

Test and Evaluation During Development and Acquisition of Materiel.

AR 600-50

Standards of Conduct for Department of the Army Personnel.

AR 611-3

Army Occupational Survey Program (AOSP).

DODD 3216.1

The Use of Animals in DOD Programs. (This publication may be obtained from the Naval Publications and Forms Center, Code 3015, 5108 Tabor Avenue, Philadelphia, PA 19120-5099.)

DODD 6465.2

Organ Disposition After Autopsy. (To obtain this directive, see the DODD 3216.1 entry above.)

MCM-1984

Manual for Courts-Martial, United States, 1984.

Note. The following United States Code (USC) statutes and Decisions of the Comptroller General (DCG) are available for reference at local installation staff judge advocate offices.

5 USC 3109

Employment of Experts and Consultants.

5 USC 5536

Extra Pay for Extra Services Prohibited.

5 USC 8100

Compensation for Work Injuries.

10 USC 980

Limitation on Use of Humans as Experimental Subjects.

10 USC 3013

Under Secretary of the Army; Assistant Secretaries of the Army.

10 USC 4503

Research and Development Programs.

10 USC 4540

Architectural and Engineering Services.

24 DCG 648.

Untitled.

24 USC 30

Payment to Donors of Blood for Persons Undergoing Treatment at Government Expense.

26 USC 501

Exemption from Tax on Corporations, Certain Trusts, etc.

45 DCG 649.

Untitled.

50 USC APP 2160

Employment of Personnel.

Section III

Prescribed Forms

DA Form 5303-R

Volunteer Agreement Affidavit. (Prescribed in para 3-5 *b* .)

Section IV

Referenced Forms

DA Form 2028

Recommended Changes to Publications and Blank Forms.

FDA Form 1571

Notice of Claimed Investigational Exemption for a New Drug. (This blank form may be obtained from the National Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.)

FDA Form 1572

Statement of Investigator (Clinical Pharmacology). (To obtain this blank form, see the FDA Form 1571 entry.)

SF 1034

Public Voucher for Purchases and Services Other Than Personal.

Appendix B

Exempted Research Categories

B-1. General

Research in which human subjects are involved in one or more of the categories listed in this appendix are exempt from this regulation.

B-2. Health care delivery and epidemiology

Health care delivery studies or routine epidemiological surveys that involve tests or procedures of no more than minimal risk. (See the glossary for the definition of an epidemiological survey.)

B-3. Educational methods

Research in educational settings that involves normal educational practices such as—

- a.* Regular and special education strategies.

- b.* The effectiveness of, or the comparison among, techniques of instruction and curricula or classroom management methods.

B-4. Educational tests

Research that involves the use of educational tests when the data are recorded in such a way that subjects cannot be identified directly or indirectly.

B-5. Public behavior

Research that involves survey, interview procedures, or the observation of public behavior (including observation by participants) except where all the following exist:

- a.* Responses or observations are recorded in such a way that subjects can be identified directly or through identifiers linked to the subject.

- b.* The subject's responses or recorded observations, if they become known outside the research, could reasonably place the subject at risk of criminal or civil liability or would damage the subject's financial standing or employability.

- c.* The research deals with sensitive aspects of the subject's behavior, such as illegal conduct, drug use, sexual behavior, or the use of alcohol.

B-6. Existing records and specimens

Research involving the collection or study of existing data, documents, records, and pathological or diagnostic specimens if these sources are publicly available or if the information is recorded in such a way that subjects cannot be identified directly or through identifiers linked to the subject.

B-7. Training

Research involving individual or group training of military personnel such as combat readiness, effectiveness, proficiency, or fitness exercises (for example, Army Training and Evaluation Program (ARTEP) and skill qualification test (SQT)). Evaluations of the training's effect on the individual participants may or may not be exempt depending on how the evaluation is made (for example, drawing of blood is not exempt).

B-8. Personnel qualified to test by duty assignment

Job related tasks of military or civilian personnel who are qualified to test by duty assignments that call specifically for such qualifications.

B-9. Other

Other research that is exempted by future changes to DHHS regulations.

Appendix C

Instructions for the Completion of the Volunteer Agreement Affidavit

C-1. General

The PI will fill in the information listed in this appendix on DA Form 5303-R in part B and inform the subject of all information entered.

C-2. Title and location

Provide the title of the study and place where it is to be conducted.

C-3. Principal investigator

Provide the name of the PI conducting the study.

C-4. Description of the study

Include a statement that the study involves research. Also provide an explanation of the purpose of the study and the expected duration of the subject's participation; a description of the procedures to be followed; an identification of any experimental procedures; and a

statement giving information about prior, similar, or related studies that provide the rationale for this study.

C-5. Risks

Include a description of any reasonably foreseeable risks or discomforts to the subject.

C-6. Benefits

Include a description of the benefits, if any, to the subject or to others that may reasonably be expected from the study. If there is no benefit to the subject, it should be so stated.

C-7. Alternative treatment

When applicable, include a disclosure of proper alternative procedures or courses of treatment, if any, that might be advantageous to the subject.

C-8. Confidentiality

Include a statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained. Also, in the case of an investigational drug or medical device protocol, include a statement noting that the FDA may inspect the records, or if the study is being performed by a contractor, a statement noting that representatives of the DOD may inspect the records.

C-9. Points of contact

Provide information on whom to contact for answers to pertinent questions about the study and the study subject's rights and whom to contact in the event of a study-related injury to the subject. This should include a name or office and the commercial and AUTOVON telephone numbers.

C-10. Subjects' rights

Include a statement that—

- a. Participation is voluntary.
- b. Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.

C-11. Compensation

For a study involving more than minimal risk, include an explanation as to whether compensation and medical treatment are available if injury occurs and, if so, what they consist of or where further information may be obtained.

C-12. Cautions

When appropriate, one or more of the elements of information below will also be given to each subject.

a. A statement that a certain treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) that are currently unforeseeable.

b. The anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

c. Additional costs to the subject that may result from participation in the study. (Retired military personnel may have their retired pay recomputed if they are paid for their participation. See paragraph 3-6 b (10)).

d. The consequences of a subject's decision to withdraw from the study and procedures for the orderly end of the subject's participation.

e. A statement that new findings developed during the course of the study that could affect the subject's willingness to continue will be given to the subject.

f. The approximate number of subjects involved in the study.

g. The precautions to be observed by the subject before and after the study.

h. If photographs are to be taken, the degree to which actions will be taken to protect the identity of the subject.

i. A statement as to whether the results of the study will be made available to the subject and if made available, in what format. In studies where subjects are in frequent contact with each other (for

example, members of small units, office coworkers, etc.), information released pertaining to the study results will not include identifiers sufficiently individualized as to allow identification of other study subjects by the person receiving the information.

C-13. Disposition of the informed consent

The PI will retain the original signed form. A copy will be provided to the volunteer. The investigator also provides a copy of the signed DA Form 5303-R to the medical records custodian for inclusion in the volunteer's medical treatment record if the volunteer agrees to its inclusion in the record. (AR 40-66, para 6-2 f, authorizes the inclusion of the form in the medical record.)

Appendix D Reporting Format for the Annual Progress Report (Clinical Investigation Program, RCS MED-300(R1))

D-1. Cover

Document the report as the "Clinical Investigation Program, RCS MED-300(R1)" to identify it as a recurring medical report.

D-2. Front matter

Include the following elements:

- a. Title page.
- b. Foreword.
- c. Table of contents.

(1) List according to hospital departments (medicine, surgery, etc.).

(2) Indicate the year the project was initiated and its present disposition: Ongoing (O), terminated (T), completed (C), submitted for publication (SP), or published (P).

D-3. Table of publications and presentations for the current fiscal year

List according to hospital department with the following identification as appropriate: (SP) submitted for publication and (C) result of an approved CI protocol.

D-4. Unit summary sheet

Report the total activities of the CIs unit, providing the following information:

- a. Objectives.
- b. Technical approach.
 - (1) Manpower.
 - (2) Funding (preceding and current fiscal year).
 - c. Progress.

D-5. Detail sheets

Report specific information of individual protocols, providing the following information:

- a. Objectives.
- b. Technical approach.
 - (1) Summary of experimental design.
 - (2) Manpower.
 - (3) Funding (preceding and current fiscal year).
 - (4) Number of subjects enrolled to date.
 - (5) Number of subjects enrolled for reporting period.
 - (6) Nature and extent of significant adverse reactions.
 - (7) Latest date of periodic review and decision to continue or discontinue study.
 - c. Progress. Summary of prior and current progress and all publications and presentations.

D-6. Back matter

Include the following elements:

- a. Index by subject and author.

b. Back cover.

Appendix E Legal Implications

E-1. Authority

The Secretary of the Army is authorized to conduct CI programs (10 USC 4503). The Secretary has the authority to “ assign, detail, and prescribe the duties ” of both members of the Army and civilian personnel of the DA (10 USC 3013(g)).

E-2. Military personnel and Department of the Army civilian employees

Compensation for the disability or death of a civilian employee resulting from personal injury or disease proximately caused by employment is payable under the Federal Employees Compensation Act (5 USC 8100 et seq.), regardless of whether employment was of a hazardous nature. The amount and type of disability compensation or other benefits payable by reason of the death or disability of a member of the Army resulting from injury or disease incident to service depends upon the individual status of each member and is covered by various provisions of law. It may be stated generally that under present laws no additional rights against the Government will result from the death or disability of military and civilian personnel participating in experiments by reason of the hazardous nature of the operations.

E-3. Private citizens

Private citizens who are not enrolled in the DEERS may not be used in CIs conducted with Major Defense Program 8 funds (see AR 37-100-FY). See AR 70-25 for a discussion on the use of private citizens in research funded by any Major Defense Program 6 funds (see AR 37-100-FY).

E-4. Use of appropriated funds for the purchase of insurance

Since the payment of insurance premiums on the life of an officer or employee of the United States is a form of compensation that is not currently authorized, payment of those premiums is prohibited. (5 USC 5536; *Commissioner of Internal Revenue v. Bonwit*, 87 F. 2d 764 (2d Cir. 1937); *Canaday v. Guitteau*, 86 F. 2d 303 (6th Cir. 1936); 24 DCG 648 (1945).)

E-5. Contractor's employees

Contractor employees who are not enrolled in the DEERS may not be used in CIs conducted with Major Defense Program 8 funds (see AR 37-100-FY). See AR 70-25 for a discussion of the use of contractor employees in research funded by Major Defense Army Program 6 funds (see AR 37-100-FY).

E-6. Irregular or fee-basis employees

Intermittent services of such employees are authorized. (For experts and consultants, see 5 USC 3109(b); sec. 710, Defense Production Act of 1960 (64 Stat. 819; 50 USC App 2160); and for architects, engineers, and other technical and professional personnel on a fee-basis, see 10 USC 4540.) Whether these employees can be detailed or assigned to the proposed experiments will depend upon the statutory authority for employment and the provisions of individual employment agreements. A final determination for these irregular and fee-basis employees for any injury or disease resulting from their employment would be made by the Federal agency responsible for deciding claims. Subject to such restrictions and limitations as may appear in the statutory authority under which an individual is employed, the Government may be legally responsible for the expense of premiums upon the life of an irregular or fee-basis employee whose rate of compensation is not fixed by law or regulations. (In this regard, the Government may provide an additional allowance to the employee for financing such private insurance arrangements as

that employee may wish to make rather than to undertake direct negotiations with insurance carriers for the desired coverage.)

Appendix F Human Use Committees

F-1. General

Before a HUC may review CIs that propose to use human subjects, its policies, procedures, and composition must be approved by HQ, HSC, for units assigned to that command or by TSG for all other units.

F-2. Membership

a. Membership will include only full-time Federally employed persons.

b. Each HUC will have at least five members. Members will have diverse backgrounds to ensure thorough review of protocols involving human volunteers as research subjects. Members should be sufficiently qualified through experience and expertise. The racial and cultural backgrounds of members and their sensitivity to such issues as community attitudes should ensure respect for their advice and counsel in safeguarding the rights and welfare of human subjects.

c. Besides having the professional competency to review protocols, the HUC will be able to determine if the proposed protocol is acceptable. Acceptability will be in terms of Army Medical Department commitments and regulations, applicable law, and standards of conduct and practice. If a HUC routinely reviews protocols that involve vulnerable categories of human subjects (for example, individuals with acute or severe physical or mental illness or individuals who are economically or educationally disadvantaged), it will include one or more persons concerned primarily with the welfare of these subjects.

d. No HUC may consist entirely of men or women.

e. Each HUC will include at least one member whose primary concerns are scientific and at least one member whose primary concerns are nonscientific (for example, lawyers, ethicists, and members of the clergy). Should a given proposal involve more than minimal risk, a physician will be included as a member of the committee.

f. Each HUC will include at least one member who is not otherwise affiliated with the institution and who is not part of the immediate family of a person affiliated with the institution. This requirement may be met by appointing a member of an institution or organizational unit not subject to the immediate authority of the approving official.

g. Except to provide information requested by the HUC, no HUC member may take part in a review of any project in which the member serves as the PI or associate investigator.

h. A HUC may invite persons with special competence to assist in the review of complex issues that require expertise beyond that available on the HUC. These persons may not vote with the HUC.

i. The approving official may not be a member. The approving official may not approve protocols for which he or she is also a PI or associate investigator. A higher echelon of command must review and approve such protocols.

F-3. Functions and operations

Each HUC—

a. Will observe written procedures for the following:

(1) Conducting the initial and continuing review of the protocol. Included would be reporting findings and actions to the investigator and the approving official.

(2) Determining those projects that must be—

(a) Reviewed more often than yearly.

(b) Verified from sources other than the investigators that no material changes have occurred since the previous HUC review.

(3) Ensuring prompt reporting to the HUC of proposed changes in the protocol. Each HUC will ensure that changes in approved

projects (during the period for which approval has already been given) are not initiated without HUC review except to eliminate immediate hazards to the subject.

(4) Ensuring prompt reporting to the HUC and approving official of unexpected problems involving risks to the subjects or others.

b. Will review proposed protocols at convened meetings except when an expedited review procedure is used—see para F-4) at which a majority of the members are present, including at least one member whose concerns are in nonscientific areas and at least one unaffiliated member. In order for the proposal to be approved, it must receive the approval of a majority of those members present at the meeting.

c. Will report to the approving official any serious or continuing noncompliance with HUC requirements and determinations found by investigators.

d. Will conduct continuing review of protocols at intervals proper to the degree of risk but not less than once per year.

e. Will have the authority to observe or have a third party observe the consent process and the investigation.

f. Will maintain a current list of HUC members. Members will be identified by name, earned degrees, and representative capacity and experience, such as board certifications and licenses. The information will be complete enough to describe each member's chief expected contributions to HUC reviews. Any employment or other relationship between members and the institution will be noted.

g. May recommend safeguards or special conditions to a protocol. If the HUC does so, the approving official may take the following action:

(1) Approve the protocol without reducing the safeguards or conditions.

(2) Require additional safeguards.

(3) Disapprove the protocol.

(4) Refer the protocol to a higher echelon approving authority and review committee.

F-4. Expedited review procedures

a. See appendix H for a list of categories of investigations that the HUC may review in an expedited review procedure.

b. See paragraph 3-5 g for the expedited review procedure that the HUC will follow.

F-5. Criteria for HUC approval of clinical investigations

a. In evaluating risks and benefits for CIs, the HUC should consider only those that may result from the investigation.

b. To approve investigations covered by this regulation, the HUC will determine that all of the requirements below are met.

(1) Risks to subjects are minimized by using procedures that are—

(a) Consistent with sound investigation design and do not unnecessarily expose subjects to risk.

(b) Already being used on the subjects for diagnosis or treatment, when appropriate.

(2) Risks to subjects are reasonable in relation to anticipated benefits to subjects.

(3) In making an assessment for the selection of subjects, the HUC should take into account the—

(a) Purpose of the investigation.

(b) Setting in which the CI will be conducted.

(4) Informed consent will be sought from each prospective subject or the subject's legally authorized representative.

(5) Informed consent will be properly documented.

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

(7) Adequate provisions exist to protect the privacy of subjects and to maintain the confidentiality of data, when appropriate.

c. Some or all of the subjects may be vulnerable to coercion or undue influence. These may be persons with acute or severe physical or mental illness or those who are economically or educationally

disadvantaged. If so, proper additional safeguards will be included in the study to protect the rights and welfare of these subjects.

F-6. Suspension or termination of approved clinical investigation

a. A HUC will have the authority to suspend or end an approved investigation that—

(1) Is not being conducted according to the HUC's requirements.

(2) Has been associated with unexpected serious harm to subjects.

b. Suspensions or terminations of investigations will include a statement of the reasons for the HUC's action. They will be reported promptly to the PI and approving official.

F-7. HUC records

a. A HUC will prepare and maintain adequate documents on HUC activities, including—

(1) Copies of all protocols approved, scientific evaluations that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries and adverse reactions.

(2) Minutes of HUC meetings documenting the date of protocol distribution to the members; the date of local approval; attendance; actions taken by the HUC; the vote on these actions, including the number of members voting for, against, and abstaining a decision; the basis for requiring changes or disapproving the investigation; and a written summary of the discussion of controversial issues and their resolution.

(3) Records of continuing review activities.

(4) Copies of all correspondence between the HUC and the investigators.

(5) A list of HUC members.

(6) Written procedures for the HUC.

(7) Statements of significant new findings.

b. The records required by this regulation will be retained permanently (see Ar 25-400-2). Such records will be reasonably accessible for inspection and copying by authorized DA personnel and representatives of the FDA.

F-8. Conflict of interest

a. It is essential that the members of the HUC continue to be perceived as and, in fact, are free from conflict of interest in their daily duties, especially with respect to the protocols that they review.

b. The issue of conflict of interest has been addressed by public law, DOD directive, and Army regulation. The situations discussed below are merely examples of *some* types of activities and relationships that may result in a conflict or the appearance of a conflict of interest.

(1) *The potential for personal or financial gain.* A committee member who is deliberating on a protocol that involves the interests of a commercial firm in which the committee member or a member of his or her immediate family is a corporate officer, stockholder, consultant, or employee has a conflict of interest and may not participate in the deliberations on that protocol.

(2) *The potential for personal reward.* A committee member who is affiliated with a protocol in the capacity of principal, associate, or coinvestigator has a conflict of interest and may not participate in deliberations of the committee on that protocol, other than to provide additional information as requested by other committee members. A committee member with such a conflict of interest must abstain from voting on the protocol.

(3) *Command influence.* It is imperative that the committee, through its members, continue to be recognized as a reasonable, deliberative body whose bias is the safety and welfare of the research subject. It is incumbent upon committee members to exercise independent, professional judgment that is free of influence from superior authority and to assure that their concerns regarding the moral, ethical, and legal issues of each protocol are answered to their satisfaction before voting on the protocol.

c. Commanders or organizational heads will establish a method

to ensure that each committee member is familiar with the pertinent laws and regulatory guidance regarding conflict of interest.

F-9. Legal review

Prior to establishing a HUC, the commander or organizational head will obtain legal counsel from the staff judge advocate (SJA). All protocols should receive legal review, either by a legal representative to the HUC or, if the HUC membership does not include a legal representative, by the local SJA, to ensure that informed consent procedures conform to State and local law.

Appendix G Guidelines for a Clinical Investigation Protocol (Exempt from report requirements per AR 335-15, para 5-2 b .)

G-1. Project title

Enter the complete project title. If an amendment, the words "Amendment to " must precede the project title.

G-2. Investigators

List the—

- a. PI.
- b. Associate investigators.

G-3. Location of study

List the facilities to be used.

G-4. Time required to complete the study

Give the month and year of the expected start and anticipated completion dates.

G-5. Introduction

a. *Synopsis*. This should include the following:

(1) A one-page summary of the proposed study similar to the abstract of a scientific paper.

(2) Major safety concerns for human subjects briefly highlighted.

b. *Medical application*. Explain briefly the medical importance and possible usefulness of the project.

c. *Objectives*. State briefly, but specifically, the objectives of the project, to include, when applicable—

- (1) Study design.
- (2) Medications used.
- (3) Type of subject population observed.

d. *Status*. State what has been accomplished or published in the proposed area of study. Describe the way in which the project will relate to, or differ from, that which has been accomplished.

e. *Bibliography*. List all references referred to in preparing the protocol.

G-6. Plan

Outline exactly what is to be accomplished in enough detail to show a clear course of action to include the technological validity of procedures and chronological steps to be taken. The plan should include the following information on the selection of subjects:

a. Number of subjects. The total number of subjects expected to complete the study.

b. Age range.

c. Sex.

d. Inclusion criteria. Specific and detailed reasons for inclusion should be presented.

e. Diagnostic criteria for entry.

f. Evaluations before entry. X ray, physical examination, medical history, hematology, chemistry, and urinalysis.

g. Exclusion criteria. A complete list detailing what subjects, diseases, and medications are excluded from the study.

h. Source of subjects. Describe briefly where subjects will be obtained.

i. Subject identification. Describe the code system used.

j. Subject assessment. Describe the method by which subjects are assigned study medications.

k. Risks and benefits analysis to subject; risks to those conducting the CI.

l. Precautions. List precautions to be taken to minimize or eliminate risks to subject.

m. Corrective action. State what corrective action is necessary if adverse reactions occur.

n. Special medical or nursing care or equipment. List care or equipment needed for subjects admitted to the project.

G-7. Project medications

Describe when applicable and include—

a. The complete name of all medications used to include control.

b. The source of all medications to include controls and lot numbers. If the medication is formulated within DA, list all components, when formulated, and manufacturing and quality control plans.

c. The place where study medications are to be stored during the study.

d. Dose range.

e. Dose schedule.

f. Radioactivity specifications.

g. Administration.

h. Pre-drug period.

i. Duration of drug treatment.

j. Accompanying medications (those allowed).

k. If needed, what antidotes must be available.

l. Labeling of study medications. (Include a copy of the label format.)

G-8. Evaluations made during and following the project

Include the evaluations listed below; it is very important to state in the protocol *who* is actually going to perform these evaluations. Evaluations may also be represented by using a project schematic.

a. Specimens to be collected.

(1) Schedule.

(2) Evaluations to be made on specimens.

(3) Storage. (Include location and if special conditions are required.)

(4) Labeling and disposition.

(5) Laboratories performing evaluations.

(6) Special precautions for subject and investigators.

b. Clinical assessments. (To include how adverse effects are to be recorded.)

c. Vital signs. When desired and frequency.

d. Followup procedures.

e. Disposition of data. (Location and duration of storage.)

f. Methods used for data collection. Critical measurements used as end points to characterize safety, efficacy, or equivalency.

g. Statistical measures in analyzing data.

h. Equipment. Describe equipment and supply requirements, costs, and resources.

G-9. Departure from protocol for individual patients

Include the following information:

a. When allowed. (Flexible but definite criteria.)

b. Who will be notified.

G-10. Adverse reactions

Include—

a. Definition of subject reactions.

b. Immediate reporting.

c. Routine reporting.

G-11. Modification of protocol

Describe the procedure to be followed if the protocol is to be modified, terminated, or extended.

G-12. Observation forms

Provide an example of all observation forms.

G-13. Disposition of unused project medications

Provide a statement pertaining to the disposition of unused medications, if applicable.

G-14. Use of information and publications arising from the study

Provide a statement of how information and publications resulting from the study are to be used.

G-15. Funding implications

Include the other department's or service's resources (time, personnel, equipment, etc.) and an indication of coordination with the affected department or service.

G-16. Medical monitor

Provide the name and telephone number of the medical monitor, when applicable.

G-17. Human use committee

Give a brief explanation of which HUC will provide initial, continuing, and annual review.

G-18. Signature

Include the signature of the appropriate approving official and the date.

G-19. Documentation

Include—

- a. Completed DA Form 5303-R. (See app C.)
- b. Institutional review of scientific and human use issues.
- c. RCC, or equivalent, and review and approval, if applicable.
- d. Radioactive drug research committee, review, and approval, if applicable.
- e. Human use approval.
- f. Animal use review and approval, if applicable.
- g. Biographical sketch of principal and associate investigators.
- h. Completed copies of the following FDA Forms, if applicable.
 - (1) FDA Form 1571 (Notice of Claimed Investigational Exemption for a New Drug).
 - (2) FDA Form 1572 (Statement of Investigator (Clinical Pharmacology)).

- (1) Weighing.
- (2) Electrocardiography.
- (3) Electroencephalography.
- (4) Thermography.
- (5) Detection of naturally occurring radioactivity.
- (6) Diagnostic echography.
- (7) Electroretinography.
- c. Does not include exposure to electromagnetic radiation outside the visible range (for example, x rays or microwaves).

H-5. Blood

Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an 8-week period and no more often than two times per week. Subjects will be 18 years of age or older, in good health, and not pregnant.

H-6. Dental plaque and calculus

Collection of both supragingival and subgingival dental plaque and calculus. The procedure must not be more invasive than routine prophylactic scaling of the teeth. The process must be accomplished according to accepted prophylactic techniques.

H-7. Voice records

Voice recordings made for research purposes such as investigations of speech defects.

H-8. Exercise

Moderate exercise by healthy volunteers.

H-9. Existing data

Study of existing data, documents, records, pathological specimens, or diagnostic specimens.

H-10. Behavior

Research on individual or group behavior or characteristics of individuals, such as studies of perception, cognition, game theory, or test development, where the investigator does not manipulate the subject's behavior and research will not involve stress to subjects.

**Appendix H
Expedited Review Categories****H-1. General**

The nine categories of studies that may be reviewed using the expedited review procedures are described in this appendix.

H-2. Hair, nails, teeth

Collection of—

- a. Hair and nail clippings in a nondisfiguring manner.
- b. Deciduous teeth.
- c. Permanent teeth if patient care indicates a need for extraction.

H-3. Excreta and secretions

Collection of excreta and external secretions including sweat, uncanalulated saliva, placenta removed at delivery, and amniotic fluid at the time of rupture of the membrane prior to or during labor.

H-4. Physical data

Recording of data from subjects who are 18 years of age or older, using noninvasive procedures routinely employed in clinical practice. This category—

- a. Includes the use of physical sensors that are applied either to the surface of the body or at a distance and do not involve input of matter or significant amounts of energy into the subject or an invasion of the subject's privacy.
- b. Includes such procedures as—

Glossary

Section I Abbreviations

AQCESS

Automatic Quality of Care Evaluation Support System

ARNG

Army National Guard

ARTEP

Army Training and Evaluation Program

ASD(HA)

Assistant Secretary of Defense (Health Affairs)

AUC

animal use committee

BAA

Broad Agency Announcement

CFR

Code of Federal Regulations

CI

clinical investigation

CIP

clinical investigation program

DA

Department of the Army

DCI

department of clinical investigation

DCSPER

Deputy Chief of Staff for Personnel

DEERS

Defense Eligibility Enrollment System

DHHS

Department of Health and Human Services

DOD

Department of Defense

DODD

Department of Defense Directive

DTF

dental treatment facility

FDA

Food and Drug Administration

FY

fiscal year

HIV

human immunodeficiency virus

HSC

U.S. Army Health Services Command

HSRRB

Human Subjects Research Review Board

HUC

human use committee

HURRAO

Human Use Review and Regulatory Affairs Office

IDE

Investigational Device Exemption

IND

Investigational Exemption for a New Drug

IRB

institutional review board

MACOM

major Army command

MCM

Manual for Courts-Martial

MEDCEN

medical center

MTF

medical treatment facility

NCI

National Cancer Institute

NDA

New Drug Application

NIH

National Institutes of Health

PCS

permanent change of station

PI

principal investigator

RCC

radiation control committee

RCS

Requirement Control Symbol

RDTE

research, development, test, and evaluation

SJA

staff judge advocate

SQT

skill qualification test

SSC—NCR

Soldier Support Center—National Capital Region

TSG

The Surgeon General

UCMJ

Uniform Code of Military Justice

USAMRDC

U.S. Army Medical Research and Development Command

USAR

U.S. Army Reserve

USD(A)

Under Secretary of Defense for Acquisition

USUHS

Uniformed Services University of the Health Sciences

Section II Terms

Adverse personnel action

For the purposes of the regulation this term includes—

- a. A court-martial.
- b. Nonjudicial punishment.
- c. Involuntary separation (other than for medical reasons).
- d. Administrative or punitive reduction in rank.
- e. Denial of promotion.
- f. An unfavorable entry in a personnel record.
- g. A bar to reenlistment.
- h. Any other action considered by the Secretary to be an adverse personnel action.

Approving official

A military commander or civilian director of an organizational element of a DA component who has been delegated authority to approve a CI protocol.

Assent

A child's affirmative agreement to participate in CIs. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Associate investigator

A person who may be involved in the execution of research but does not have overall responsibility. The FDA refers to such individuals as subinvestigators.

Clinical investigation

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

Clinical investigation committee

A committee appointed by the commander to review, before HUC review, CI protocols for scientific adequacy to set priorities for support and to make recommendations. This committee may be consolidated with a HUC.

Clinical trial

The research process necessary to gain marketing approval of an investigational drug or device.

Consent

See informed consent.

Donor

An individual, organization, or corporation that gives funds, services, or tangible or intangible property to the Government without any compensation or promise of compensation.

Epidemiologic-assessment interview

For the purposes of this regulation, the term means the questioning of a seropositive soldier for medical treatment or counseling or for epidemiologic or statistical purposes.

Epidemiological surveys

For the purpose of this regulation, the term means studies involving no more than minimal risk on the distribution and determinants of the frequency of disease in humans in which the study data are not linked to personal identifiers. Epidemiological surveys focus on the “ills” of a population rather than on persons.

Expedited review procedures

Those procedures used in certain kinds of investigations involving no more than minimal risk and those used for minor changes in approved investigations (see app H).

Experimental subject

See Human subject.

Gifts

Any donation of funds, services, or tangible or intangible property from a non-DOD source for which there is no compensation or promise of compensation on behalf of the donor.

Grant

An award of funds, services, or tangible or intangible property from a nonprofit organization or Federal agency in support of the CIP that is pursuant to a written agreement.

Grantor

Any corporation, foundation, trust, or institution that is operated for the purpose of higher learning or research, is not organized for profit, and does not provide any net earnings to shareholders or individuals.

Health and Human Services Certificate of Assurance

A document issued by the Office for Protection From Research Risk, DHHS, in which that office acknowledges that a research institution has established policies and procedures consistent with Federal regulations (app A). Research institutions must have this certificate in order to receive research funds from the NIH.

Health care delivery studies

Application of scientific methods to the study of the availability, organization, administration, and management of health services. The

efficiency and effectiveness with which such services are delivered are included.

Health care personnel

Military personnel, civilian employees, or contract personnel (including military and civilian staff members assigned to, employed by, or appointed to the USUHS) who provide patient care or patient care support services in military MTFs and DTFs.

Human subject

a. A living individual about whom an investigator conducting CI or research obtains data through interaction with the individual, including both physical procedures and manipulations of the subject or the subject's environment. The term does not include military or civilian personnel who are qualified to test by assignment to duties that call specifically for such qualifications such as test pilots and test engineers.

b. Minor (child). A person who has not attained the legal age for consent to treatments or procedures involved in clinical research under the applicable laws and jurisdiction in which the CI will be conducted.

c. Human subjects may be thought of as direct objects when the research is to determine the effects of a new system on humans (for example, the effects of a weapon's blast on hearing) or as indirect objects when a test is conducted to determine how humans affect the ultimate performance of a system (doctrine, concepts, training programs).

Human Subjects Research Review Board

The principal body of the Office of The Surgeon General for review of CI and research activities.

Human use committee

A body set up to provide initial and continuing review of CIs involving the use of human subjects. A HUC is fundamentally similar to an IRB established under Federal regulations (app A) but has somewhat different authority as compared to an IRB. Within the DOD, authority to approve the use of human subjects in CI is vested in commanders. Commanders act on the recommendations of validly constituted HUCs. Outside DOD, IRBs tend to be vested with this authority. Appendix F describes the membership, functions, and operations of a HUC.

Informed consent

The legally effective agreement of the subject or the subject's legally authorized representative for the subject to participate in CIs covered by this regulation. Informed consent includes, when appropriate, those elements listed in appendix C of this regulation.

a. *Permission.* The agreement of parent(s) or guardian to the participation of their child or ward in CI.

b. *Guardian.* An individual who is authorized under applicable State or local law

to consent on behalf of a minor (child) to general medical care.

c. *Assent.* A minor's (child's) affirmative agreement to participate in CI. Mere failure to object should not, absent affirmative agreement, be construed as assent.

Institution

Any public or private entity or agency (including Federal, State, or other agencies).

Investigational drug

A drug may be considered investigational when the composition is such that—

a. Its proposed use is not recognized for the use under the conditions prescribed, or its proposed use is not recommended or suggested in its approved labeling. Experts qualified by scientific training and experience evaluate the safety and effectiveness of drugs to make this determination.

b. Its use has become recognized as investigational as a result of studies to determine its safety and effectiveness for use under such conditions.

Investigational medical device

a. A device that is not generally used in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans, and recognized as safe and effective.

b. Research is usually, but not necessarily, initiated to determine if the device is safe or effective.

Legally authorized representative

A person or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's taking part in the procedures involved in the CI.

Major Defense Program 6 Funds

Funds appropriated to the DOD to conduct research by RDTE activities. (See AR 37-100-FY.)

Major Defense Program 8 Funds

Funds appropriated to the DOD to provide health care. (See AR 37-100-FY.)

Medical device

Any instrument, apparatus, or other similar or related article, including component, part, or accessory that—

a. Is recognized in the National Formulary or United States Pharmacopeia or any supplement thereto; and

b. Is intended for use in the diagnosis of disease or other conditions or in the cure, mitigation, treatment, or prevention of disease in man or other animals; or

c. Is intended to alter the structure or function of the body of man or other animals; and

d. Does not achieve any of its principal intended purposes through chemical action within or on the body of man or other animals and is not dependent upon being metabolized for the achievement of any of its principal intended purposes.

Medical monitor

This person is a military or DA health care provider qualified by training, experience, or both, to monitor human subjects during the conduct of CIs. This person is an advocate for the medical safety of the volunteers and as such will not be an investigator involved in the protocol.

Minimal risk

The proposed risks are not considered greater than those encountered in the subject's daily life or during routine physical or psychological examinations.

New Drug Application

Documentation submitted to the FDA that is intended to demonstrate the safety and effectiveness of the drug in order to obtain approval to market the drug in the United States.

Non-U.S. citizens

Foreign nationals excluding personnel on active duty.

Personal identifier

A method or system that links data to the individual from whom or about whom it pertains.

Principal investigator

A uniformed or civilian individual who is assigned or employed in an MTF, DTF, USUHS, or other DOD research facility and who is responsible for the innovation, experimental design, generation, and analysis of data, presentation of reports, and protection of human subjects in the performance of a CI study.

Protocol

The written, detailed plan by which clinical investigation is to be conducted. (See app G for an example of a CI protocol.) The plan contains, as a minimum—

- a. The objectives of the project.
- b. The information to be collected and the means by which it will be collected and evaluated.
- c. An assessment of potential risk and benefits to subjects and of safety measures and other means to be used to reduce risk to subjects.

Radioactive drug research committee

A committee appointed by the commander and approved by the FDA to review and approve the conditions under which radioactive drugs having neither an IND nor an approved NDA that are intended for human subject research are considered safe and effective.

Radioisotope/radiation control committee

A committee appointed by the commander to ensure that individual users of radioactive materials within the medical facility and each radionuclide used will be approved and controlled. The approval and control is in accordance with the requirements specified in the conditions of the Nuclear Regulatory

Commission license, DA radioactive material authorization, and appropriate Federal directives.

Research

A systematic scientific investigation designed to develop or contribute to generalizable knowledge. DOD Directive 3216.2 states that the term does not include individual or group training of military personnel in skills such as combat readiness, effectiveness, and proficiency or fitness exercises.

Research, development, test, and evaluation

Includes those categories of research and development included in Major Defense Program 6 (see AR 37–100–FY), Research and Development, and operational systems development contained in the Five-Year Defense Program.

Schedule I controlled drug substances

Any drug or substance by whatever official name, common or usual name, chemical name, or brand name listed in AR 40–7 and 21 CFR 1308 (see the FDA Regulation entry in app A); for example, heroin.

Significant risk device

A device that presents potential for serious risk to health safety or welfare of the subject. Such a device is intended as an implant; is to be used in supporting or sustaining human life; or is of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing the impairment of human health. Examples of such devices are pacemakers and some laser and hemodialysis systems.

Subinvestigator

See associate investigator.

Test

A process by which data 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. See AR 70–10 for a more detailed discussion of the RDTE type tests.

Section III**Special Abbreviations and Terms**

There are no special terms.

VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 70-25 or AR 40-38; the proponent agency is OTSG

PRIVACY ACT OF 1974

- Authority:** 10 USC 3013, 44 USC 3101, and 10 USC 1071-1087.
- Principle Purpose:** To document voluntary participation in the Clinical Investigation and Research Program. SSN and home address will be used for identification and locating purposes.
- Routine Uses:** The SSN and home address will be used for identification and locating purposes. Information derived from the study will be used to document the study; implementation of medical programs; adjudication of claims; and for the mandatory reporting of medical conditions as required by law. Information may be furnished to Federal, State and local agencies.
- Disclosure:** The furnishing of your SSN and home address is mandatory and necessary to provide identification and to contact you if future information indicates that your health may be adversely affected. Failure to provide the information may preclude your voluntary participation in this investigational study.

PART A(1) - VOLUNTEER AFFIDAVIT

Volunteer Subjects in Approved Department of the Army Research Studies

Volunteers under the provisions of AR 40-38 and AR 70-25 are authorized all necessary medical care for injury or disease which is the proximate result of their participation in such studies.

I, _____, SSN _____, having full capacity to consent and having attained my _____ birthday, do hereby volunteer/give consent as legal representative for _____ to participate in _____

(Research study)

under the direction of _____ conducted at _____

(Name of Institution)

The implications of my voluntary participation/consent as legal representative; duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by _____

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights/the rights of the person I represent on study-related injury, I may contact _____

at _____ *(Name, Address and Phone Number of Hospital (Include Area Code))*

I understand that I may at any time during the course of this study revoke my consent and withdraw/have the person I represent withdrawn from the study without further penalty or loss of benefits; however, I/the person I represent may be required (military volunteer) or requested (*civilian volunteer*) to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my/the person I represent's health and well-being. My/the person I represent's refusal to participate will involve no penalty or loss of benefits to which I am/the person I represent is otherwise entitled.

PART A (2) - ASSENT VOLUNTEER AFFIDAVIT (MINOR CHILD)

I, _____, SSN _____, having full capacity to assent and having attained my _____ birthday, do hereby volunteer for _____ to participate in _____

(Research Study)

under the direction of _____ conducted at _____

(Name of Institution)

(Continue on Reverse)

PART A(2) - ASSENT VOLUNTEER AFFIDAVIT (MINOR CHILD) (Cont'd.)

The implications of my voluntary participation; the nature, duration and purpose of the research study; the methods and means by which it is to be conducted; and the inconveniences and hazards that may reasonably be expected have been explained to me by

I have been given an opportunity to ask questions concerning this investigational study. Any such questions were answered to my full and complete satisfaction. Should any further questions arise concerning my rights I may contact

at _____
(Name, Address, and Phone Number of Hospital (Include Area Code))

I understand that I may at any time during the course of this study revoke my assent and withdraw from the study without further penalty or loss of benefits; however, I may be requested to undergo certain examination if, in the opinion of the attending physician, such examinations are necessary for my health and well-being. My refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled.

PART B - TO BE COMPLETED BY INVESTIGATOR

INSTRUCTIONS FOR ELEMENTS OF INFORMED CONSENT: (Provide a detailed explanation in accordance with Appendix C, AR 40-38 or AR 70-25.)

I do do not (check one & initial) consent to the inclusion of this form in my outpatient medical treatment record.

SIGNATURE OF VOLUNTEER	DATE	SIGNATURE OF LEGAL GUARDIAN (If volunteer is a minor)	
PERMANENT ADDRESS OF VOLUNTEER	TYPED NAME OF WITNESS		
	SIGNATURE OF WITNESS		DATE

Unclassified

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