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Headquarters
Department of the Army
Washington, DC
15 April 1984

*Army Regulation 40–38

Effective Date 15 May 1984

Medical Services

# Clinical Investigation Program

**Summary.** This regulation implements DOD Directive 3216.2 (Protection of Human Subjects in DOD-Supported Research) It reflects the present legal requirements, which are continually changing, for the Clinical Investigation Program. Excluding situations where approval authority is limited, authority to approve clinical investigations using human subjects can be delegated within the military chain of command to the lowest level operating a human-subjects review process.

**Applicability.** This regulation applies to all Army medical facilities except those funded under research, development, test, and evaluation (RDTE) appropriations. It does not apply to the US Army Reserve and the Army National Guard, nor to health care delivery studies or routine epidemiological surveys that involve tests or procedures of no more than minimal risks.

**Impact on New Manning System.** This regulation does not contain information that affects the New Manning System

**Supplementation.** Supplementation of this regulation is prohibited unless prior approval is obtained from HQDA (DASG–RDZ), WASH DC 20310

**Interim changes.** Interim changes to this regulation are not official unless they are authenticated by The Adjutant General Users will destroy interim changes on their expiration dates unless sooner superseded or rescinded.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, US Army Medical Research* and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21701. Users within the United States Army Health Services Command (HSC) will forward DA Form 2028 through Commander, US Army Health Services Command, ATTN: HSHN–I, Fort Sam Houston, TX 78234.

## Contents



This regulation supersedes AR 40–38, 23 February 1973.

# Chapter 1
# Introduction

## 1-1. Purpose

This regulation—

*a*. Prescribes Army policy on the conduct of clinical investigations to include—

(1) Command responsibilities.

(2) Review process requirements.

(3) Approval authorities.

(4) Reporting requirements.

*b*. Establishes a decentralized approval authority for those commanders having a formal protocol review process.

## 1-2. Exemptions

Clinical investigations are exempt from this regulation when the only involvement of human subjects is in one or more of the following:

*a*. Health care delivery studies or routine epidemiological surveys that involve tests or procedures of no more than minimal risk.

*b*. Investigations conducted in established or commonly accepted educational settings, involving normal educational practices, such as investigations on—

(1) Regular and special education instructional strategies, or

(2) The effectiveness of, or the comparison among, instructional techniques, curricula, or classroom management methods.

*c*. Investigations involving the use of educational tests if information taken from these sources is recorded in such a way that subjects cannot be identified directly or through identifiers linked to the subjects. (Tests may be classified as diagnostic, aptitude, or achievement.)

*d*. Investigations involving survey or interview procedures except when all of the conditions below exist.

(1) The responses are recorded in such a way that the human subjects can be identified directly or through identifiers linked to the subjects.

(2) The subject's responses, if they become known outside the investigation, could reasonably place the subject at risk of criminal or civil liability, or be damaging to the subject's financial standing or employability.

(3) The investigation deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

*e*. Investigations involving the observation (including observation by participants) of public behavior, except when all of the conditions below exist.

(1) The observations are recorded in such a way that the human subjects can be identified directly or through identifiers linked to the subjects.

(2) The observations recorded about the person, if they become known outside the investigation, could reasonably place the subject at risk of criminal or civil liability, or be damaging to the subject's financial standing or employability.

(3) The investigation deals with sensitive aspects of the subject's own behavior such as illegal conduct, drug use, sexual behavior, or use of alcohol.

*f*. Investigations involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens if—

(1) These sources are publicly available, or

(2) The information is recorded by the investigator in such a way that subjects cannot be identified directly or through identifiers linked to the subjects.

*g*. Other investigations which are exempted in the future by the Department of Health and Human Services (HHS) or The Surgeon General (TSG).

## 1-3. References

Required and related publications are listed in appendix A.

## 1-4. Explanation of abbreviations and terms

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

## 1-5. Limitations of authority

*a*. Nothing in this regulation limits the authority of a health care practitioner to provide emergency care under laws that apply in the jurisdiction in which they are provided.

*b*. Approval authority for studies involving deliberate exposure of human subjects to nuclear weapons effect or chemical warfare agents is limited to the Under Secretary of Defense for Research and Engineering or his or her designee.

*c*. Only The Surgeon General (TSG) has approval authority for studies involving human subjects using Schedule I controlled drug substances.

*d*. Only TSG has approval authority for investigations involving minors when—

(1) Any usual permission requirement has been waived.

(2) Subjects are wards of a State or any other agency, institution, or entity.

*e*. Only the Deputy Chief of Staff for Personnel (DCSPER) has approval authority for studies involving alcohol and drug abuse programs.

# Chapter 2
# Responsibilities

## 2–1. Assistant Secretary of Defense (Health Affairs)

The Assistant Secretary of Defense (Health Affairs) will serve as the DOD representative on matters relating to implementation of the Food and Drug Administration's regulatory requirements.

## 2–2. Deputy Chief of Staff for Personnel (DCSPER)

The DCSPER has approval authority for all studies of alcohol and drug abuse programs.

## 2–3. The Surgeon General (TSG)

TSG will—

*a*. Issue policies and draft regulations on clinical investigations.

*b*. Except when limited by this regulation, take final action on proposals submitted for TSG approval.

*c*. Provide human use review of protocols submitted for approval, as required by paragraphs 1–5*b* and 1–5*e* above, to—

(1) The Under Secretary of Defense for Research and Engineering.

(2) DCSPER.

*d*. Take final action on clinical investigation proposals from medical treatment facilities (MTFs) not in a major Army command (MACOM) with an established internal protocol review process.

*e*. Establish, under the Commander, US Army Medical Research and Development Command (USAMRDC), the Human Use Review Office (HURO).

*f*. Establish, under the Assistant Surgeon General for Research and Development, the Human Subjects Research Review Board (HSRRB).

*g*. When appropriate, direct medical followup on subjects of clinical investigation to insure that any long-range problems are detected and treated.

*h*. Approve those protocols required by paragraphs 1–5*c* and 1–5*d* above.

*i*. Exempt classified studies from being filed under a "Notice of Claimed Investigational Exemption for a New Drug" to the Food and Drug Administration.

*j*. Report on a frequent basis findings associated with paragraph 2–3*i* above to the United Secretary of Defense for Research and Engineering and the Assistant Secretary of Defense (Health Affairs).

*k*. Report on a frequent basis unclassified findings associated with paragraph 2–3*i* above to the Food and Drug Administration.

## 2–4. Commanders of major Army commands (MACOMs)

When a clinical investigation is proposed, the MACOM commander may implement the actions below or use the established review process through TSG's HSRRB.

*a*. Promote, manage, and support the performance of clinical investigations, realizing the importance of organizing investigations where postgraduate educational programs are conducted.

*b*. Publish proper directives and regulations to implement the policies and guidance provided in this regulation.

*c*. Establish the format for preparation of proposed clinical investigation studies. (See app B.)

*d*. Establish the format and reporting requirements reflecting the scope, nature, and status of clinical investigation efforts during each fiscal year. (See app C.)

*e*. Publish proper directives and regulations to insure that adequate documents are maintained on human subjects used in clinical investigations, including resulting adverse reactions.

*f*. Forward one copy of these directives and regulations to Commander, US Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21701. The copies will be sent within 60 days of publication.

## 2–5. Commanders of major Army medical commands

*a*. Commanding General, US Army Health Services Command (CG, HSC). The CG, HSC will—

(1) Comply with paragraph 2–4.

(2) Establish within the US Army Health Care Studies and Clinical Investigation Activity the Clinical Investigation Program Division to coordinate and monitor clinical investigation program activity and serve as point of contact (POC) for policies and regulations on human use in clinical investigation.

(3) Insure that commanders of Army medical centers within HSC—

*(a)* Are responsible for all clinical investigations conducted within the medical center (MEDCEN).

*(b)* Organize a clinical investigation support system within a separate hospital organizational structure. This system will implement the Clinical Investigation Program (CIP).

*(c)* Appoint a consolidated or separate Clinical Investigation Committee (CIC) and a Human Use Committee (HUC) (app D) and, where appropriate, an Animal Use Committee (AUC).

*b*. Commanders of other major medical commands (overseas). When a clinical investigation is proposed, the commander of a major Army medical command (overseas) will comply with the proper parts of paragraphs 2–4 and *a* above.

### 2–6. Commanders of medical treatment facilities (MTFs), other than medical centers

Commanders of MTFs, other than medical centers, may—

*a*. Organize, within their authorized and available resources, support for clinical investigations.

*b*. Establish advisory committees and a review process as discussed in this regulation.

### 2–7. Human Subjects Research Review Board (HSRRB)

The HSRRB will—

*a* Evaluate methods by which the Department of the Army (DA) uses human subjects in clinical investigations.

*b*. Recommend policy to TSG to maintain the quality of investigations consistent with contemporary moral, ethical, and legal standards.

*c*. Evaluate clinical protocols submitted to TSG for approval.

*d*. Maintain adequate documents of approved protocols. Include resulting adverse reactions to clinical investigations at MTFs not in a MACOM with an established internal review process.

### 2–8. Chief, Human Use Review Office (HURO)

The Chief, HURO will—

*a*. Provide, for TSG, administrative support for the HSRRB.

*b*. Initiate a review of all protocols submitted to TSG for approval.

*c*. Prepare and submit DA-sponsored Notice of Claimed Investigational Exemption for a New Drug (IND) and Investigational Device Exemptions (IDEs) for those held by DA directly to the Food and Drug Administration.

*d*. Serve as the POC for information regarding policies and regulations on human use for TSG.

### 2–9. Principal Investigator

The principal investigator will—

*a*. Insure that adequate records are maintained on—

(1) Receipt, storage, use, and disposition of all investigational drugs and devices in accordance with AR 40–7.

(2) All observations and other data important to the study.

*b*. Prepare annual progress reports and others as determined by the approving authority and regulatory agencies.

*c*. Promptly notify the approving authority, through the HUC, of adverse effects reasonably caused by the investigation.

*d*. Insure that the investigation has been approved by the proper review committee before starting, changing, or extending the study.

*e*. Insure that all subjects, including those used as controls, or their representatives, are fully informed of the nature of the investigation, to include potential risks to the subject.

*f*. Insure that investigational drugs or devices are used only under—

(1) His or her personal supervision, or

(2) The supervision of previously approved associate investigators.

# Chapter 3
# Clinical Investigations

## 3–1. Policy

*a.* Army Medical Department (AMEDD) commanders will encourage the performance of clinical investigations. Personnel assigned to MTFs within HSC where postgraduate educational programs are conducted will especially encourage such investigations.

*d.* The degree of potential risk will never exceed the expected benefits of the study.

*c.* Human subjects are volunteers in the sense that they have a fundamental right to choose, within the limits of their legal and mental capacities, as to whether or not to take part as human subjects. This freedom of choice applies also to military personnel and as such they are *not* subject to punishment under the Uniform Code of Military Justice (UCMJ) for choosing not to take part as human subjects. Further, no administrative sanctions will be taken against military or civilian personnel for choosing not to take part as human subjects.

*d.* Within Army hospitals, the commander will—

(1) Protect human subjects.

(2) Maintain adequate personnel and resources support for the CIP.

*e.* Moral, ethical, and legal concepts on the use of human subjects will be followed as outlined in this regulation.

*f.* Only persons who are fully informed and voluntarily agree to take part may be used as human subjects in clinical investigations except—

(1) When the measures used are intended to be beneficial to the recipient and permission is obtained from a legal representative on the recipient's behalf.

(2) When, in the judgment of a physician, emergency medical care is rendered to the extent permitted under applicable law.

*g.* Clinical investigations may be conducted outside the United States that involve non-US citizens as human subjects. If so, the laws, customs, and practices of the country in which the research is conducted will take precedence over procedures required by this regulation. The investigation must meet the same standards of ethics and safety that apply to research conducted within the United States involving US citizens. When standards vary, the more stringent ones will apply. The minimum age for consent for US citizens taking part in clinical investigations outside the United States is 18, regardless of the laws of the country that may pertain to its native citizens.

*h.* The use of prisoners of war and detainees as human subjects of clinical investigation is prohibited.

*i.* Volunteers will be authorized all necessary medical care for injury or disease that is the proximate result of their taking part in approved Army clinical investigations.

*j.* Subjects must be given adequate time to review and understand all information before agreeing to take part in the study. The agreement document will be written in language that is easily understood by the subject.

*k.* The subject's agreement will be documented on DA Form 5303–R (Volunteer Agreement Affidavit) If additional pages are needed to support DA Form 5303–R, each page will be initialed by both the subject and witness. This form is not appropriate for assent (see glossary). When applicable, assent documentation will be recommended by the Human Use Committee (HUC) and approved by the commander. (A copy of DA Form 5303–R is located at the back of this regulation for local reproduction.)

*l.* Clinical investigations on medical devices will be conducted under part 812, title 21, Code of Federal Regulations (CFR). A command does not have to submit an Investigational Device Exemption (IDE) to the Food and Drug Administration if the device to be investigated does not pose a significant risk.

*m.* Contractors or grantees holding an assurance of compliance with HHS will be considered in compliance with this regulation. In the absence of such an assurance, a special assurance will be negotiated with the contractor or grantee.

*n.* Requests for exceptions to policy as stated in this regulation will be submitted to Commander, US Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21701. Requests will be fully justified. TSG's HSRRB will evaluate the requests. They will then be forwarded to the Under Secretary of Defense for Research and Engineering for review.

*o.* A human-subjects study will be designed to achieve its stated objectives. The proposed number of subjects will be the minimum needed to insure that statistically significant results are obtained.

*p.* The human-subjects study will be conducted 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 studies will *not* be conducted if any reason exists to believe that death or injury will result.

*q.* Only persons judged qualified by the appropriate approving authority will conduct human-subjects studies.

*r.* Resource requirements for the CIP will be programed and budgeted through established program budget procedures. Clinical investigators are encouraged to contact Commander, USAMRDC, ATTN: SGRD–OP, Fort Detrick, Frederick, MD 21701, to determine whether health problems encountered in active

duty military personnel may be investigated with resources provided by USAMRDC.

*s*. Investigation objectives should allow for the conclusion of a study within the tour of the investigator. If this is not possible, careful plans should be made to permit continuation of the study when the investigator leaves.

*t*. A subject's costs while in the hospital will be waived if he or she normally would not enter the hospital for treatment but is requested to do so for clinical investigation. (These costs would include per diem.) This policy applies to a subject's extended time in a hospital for clinical investigation when he or she is already in the hospital (since the extended time in the hospital is for the Army's benefit). Subsistence costs will be included as part of the protocol costs.

*u*. Minors may be used as human subjects in clinical investigations only when all the conditions below are met.

(1) The risk is justified by the anticipated benefit.

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

(3) A legally authorized representative has granted written permission for the minor to participate in the study.

(4) The minor, if capable of assenting, has assented in writing. In determining whether the minor is capable of assenting, the HUC will consider the minor's age and maturity. This judgment may be made for all minors involved in the study, or for each child, individually as the HUC deems proper.

(5) Mere failure to object should not, in the absence of affirmative agreement, be construed as assent.

*v*. Protocol policy is as follows:

(1) Each approved protocol will be reviewed at least yearly and on a continuing basis as determined by the HUC.

(2) Protocols for the use of drugs or Schedule I controlled substances for investigational purposes will be approved according to AR 40–7.

(3) When applicable, the Radioactive Drug Research Committee, or equivalent, will review protocols before HUC review.

*w*. Reprints of articles based on approved clinical investigation projects are official material as defined in AR 70–14, paragraph 3. Purchase of such reprints will be made from Operation and Maintenance, Army (OMA) funds.

*x*. If it is determined that risk in a human-subjects investigation is more than minimal, a medical monitor will be recommended by the HUC and appointed by the commander.

*y*. The medical monitor has authority to end the study if—

(1) The subjects are at risk of life or limb, or

(2) It appears that the risk to the subjects is significantly greater than anticipated at the time of review and approval of the investigation.

*z*. The principal investigator or associate investigator may also function as a medical monitor.

*aa*. Emergency use of an investigational drug or device will be in accordance with AR 40–7.

## 3–2. Procedures

*a*. MACOMs with an established internal review program will forward the following items to Commander, US Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21701:

(1) One copy of the implementing directives and regulations pertaining to clinical investigations.

(2) Two copies of clinical investigation annual progress reports.

(3) When higher approval authority is needed, two copies of the protocol, together with all the minutes of committees reviewing the study, and a completed DA Form 5303–R.

*b*. MACOMs without an established internal review process will forward the following items to Commander, US Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21701:

(1) Two copies of the proposed protocol, together with the commander's recommendations and a completed DA Form 5303–R.

(2) Three copies of clinical investigation annual progress reports.

*c*. HUCs are set up according to the procedures outlined in appendix D.

*d*. The expedited review procedure is used as follows:

(1) Appendix F contains a list of investigations that the HUC may review through an expedited review procedure. The HUC may review some or all of the investigations appearing on the list through an expedited review procedure if the investigation involves no more than minimal risk.

(2) The HUC may also use the expedited review procedure to review minor changes in previously approved investigations during the period for which approval is authorized. Under an expedited review procedure, the HUC chairperson, or one or more experienced reviewers designated by the chairperson from among members of the HUC may carry out the review. The reviewers of the investigation may exercise all of the authorities of the HUC except that of disapproval. An investigation may be disapproved only after review according to the nonexpedited procedure in paragraph D–2*b*.

(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.

# Appendix A
# References

## Section I
## Required Publications

AR 40–7 (Use of Investigational Drugs in Humans and the Use of Schedule I Controlled Drug Substances). Cited in paragraphs 2–9*a*(1), 3–1*v*(2), and 3–1*aa*.

AR 70–14 (Publication and Reprints of Articles in Professional Journals). Cited in paragraph 3–1*w*.

AR 340–18 (The Army Functional Files System). Cited in paragraph D–6*b*.

## Section II
## Related Publications*

AR 70–18 (The Use of Animals in DOD Programs).

AR 70–25 (Use of Volunteers as Subjects of Research).

AR 340–21 (The Army Privacy Program).

DODD 3216.2 (Protection of Human Subjects in DOD-Supported Research). Department of Defense Directives are available from HQDA (DAAG–OPA), WASH DC 20310, telephone AUTOVON 227-1388.)

DODD 6000.4 Department of Health and Human Services Regulation (Clinical Investigation Program). (Protection of Human Subjects (45 CFR Part 46)). (Code of Federal Regulations listed in this regulation are available from the Superintendent of Documents, Government Printing Office, WASH DC 20402.)

Food and Drug Administration Regulation (21 CFR subchapters A, D, and H).

Memorandum of Understanding Between the Food and Drug Administration and the Department of Defense (Investigational Use of Drugs by Department of Defense, November 21, 1974). (This publication is available from Commander, US Army Medical Research and Development Command, ATTN: SGRD–HR, Fort Detrick, Frederick, MD 21701, telephone AUTOVON 343-2165.)

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

# Appendix B
# Guideline for an Application for a Non-Food and Drug Administration Clinical Investigation Using Investigational Drugs (Exempt requirement, AR 335–15, para 7–2b.)

## B–1. Project title
Enter the complete project title. If an amendment, the words "Amendment to . . ." must precede the project title.

## B–2. Investigators
*a.* Principal investigator.
*b.* Associate investigators.

## B–3. Location of study
List of facilities to be used.

## B–4. Time required to complete the study
Give month and year of expected start and anticipated completion date.

## B–5. Introduction
*a. Synopsis.*
(1) One-page summary of 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.

## B–6. Plan
Outline exactly what is proposed to be accomplished in enough detail to show a clear course of action to include technological validity of procedures and chronological steps to be taken. The plan should include the following minimum information on 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, 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 by what method subjects are assigned study medications.
*k. Risks and benefits* analysis to subject; risks to those conducting the clinical investigation.
*l. Precautions.* List precautions to be taken to minimize or eliminate risks to subject.
*m. Corrective action.* State corrective action necessary if adverse reactions occur
*n. Special medical or nursing care or equipment.* List care or equipment needed for subjects admitted to the project.

## B–7. Project medications
(Describe when applicable.)
*a. Complete name* of all medications used to include control.
*b. Source* of all medications to include controls and lot numbers. If medication is formulated within DA, list all components, when formulated, and manufacturing and quality control plans.
*c. 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.)

## B–8. Evaluations made during and following project
(Evaluation may also be represented by using a project schematic.)

*Note.* It is very important to state in the protocol *who* is actually going to perform the evaluations below.
*a. Specimens* to be collected.
(1) *Schedule.*

(2) *Evaluations* to be made on specimens.

(3) *Storage*. Where, 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. Where it is stored and for how long.

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

*g*. *Statistical measures* in analyzing data.

### B–9. Departure from protocol for individual patients

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

*b*. *Who* will be notified.

### B–10. Adverse reactions

*a*. *Definition* of subject reactions.

*b*. *Immediate reporting*.

*c*. *Routine reporting*.

### B–11. Modification of protocol

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

### B–12. Example of all observation forms

### B–13. Statement pertaining to the disposition of unused project medications, if applicable

### B–14. Use of information and publications arising from the study

### B–15. Special or unusual funding implications

### B–16. Medical monitor

(When applicable, the name and telephone number of the medical monitor.)

### B–17. Human Use Committee

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

### B–18. Signature of appropriate approving official and date

### B–19. Documentation

*a*. *Completed DA Form 5303–R*. (See app E.)

*b*. *Institutional review* of scientific and human use issues.

*c*. Radioisotope and Radiation Control Committee, or equivalent, *review and approval*, if applicable.

*d*. *Human use* approval.

*e*. *Animal use* review and approval, if applicable.

*f*. *Biographical sketch* of principal and associate investigators.

*g*. *Completed copies* of the following FDA Forms, if applicable. (Blank copies of the below listed forms are available from the National Center for Drugs and Biologics, Food and Drug Administration, 5600 Fishers Lane, Rockville, MD 20857.)

(1) FDA Form 1571 (Notice of Claimed Investigational Exemption for a New Drug).

(2) FDA Form 1572 (Statement of Investigator (Clinical Pharmacology)).

(3) FDA Form 1573 (Statement of Investigator).

# Appendix C
# Reporting Format for Annual Progress Report (RCS MED–300 (R1))

## C–1. Front cover
Document the report as the "Clinical Investigation Program, RCS MED–300(R1)" to identify it as a recurring medical report.

## C–2. Title page

## C–3. Foreword

## C–4. Table of contents
*a.* List according to hospital departments (Medicine, Surgery, etc.).

*b.* Indicate year project was initiated and its present disposition: Ongoing (O), Terminated (T), Completed (C), Submitted for Publication (SP), or Published (P).

## C–5. Table of publications and presentations for current fiscal year
List according to hospital department.

## C–6. Unit summary sheet
Report the total activities of the clinical investigations unit.

*a. Objectives.*

*b. Technical approach.*

(1) Manpower.

(2) Funding (preceding and current fiscal year).

*c. Progress.*

## C–7. Detail sheets
Report specific information of individual protocols

*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 publication(s) and/or presentation(s).

## C–8. Index

*a. Subject.*

*b. Author.*

## C–9. Back cover

# Appendix D
# Human Use Committee (HUC)

## D–1. 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 promote complete and adequate review of clinical investigation activities commonly conducted in the Clinical Investigation Program. 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 promote respect for their advice and counsel in safeguarding the rights and welfare of human subjects.

*c.* Besides having the professional competency to review specific clinical investigations, the HUC will be able to determine if proposed investigations are acceptable. Acceptability will be in terms of AMEDD commitments and regulations, applicable law, and standards of conduct and practice. A HUC may regularly review investigations that involve vulnerable categories of subjects. Therefore, it will include one or more persons concerned primarily with the welfare of these subjects.

*d.* Normally, no HUC may consist entirely of men or women, or members of one profession. The approving official may waive this requirement in those cases in which compliance is impractical.

*e.* Each HUC will include at least one member whose primary concerns are nonscientific; for example, lawyers, ethicists, and members of the clergy. The approving authority, or HUC itself, may have reason to believe a given proposal includes more than minimal risk. If so, a physician will be included as an *ad hoc* 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. The requirement for a nonaffiliated member 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 may have a member taking part in its initial or continuing review of any project in which the member has a conflict of interest.

*h.* A HUC may, at its discretion, 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 clinical investigations for which he or she is also a principal or associate investigator. A higher echelon of command must review and approve such research projects.

## D–2. Functions and operations

Each HUC—

*a.* Will follow written procedures for—

(1) Conducting its initial and continuing review of clinical investigation; reporting its findings and actions to the investigator and the approving official.

(2) Determining those projects that—

*(a)* Require review more often than yearly.

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

(3) Insuring prompt reporting to the HUC of proposed changes in an investigation; insuring changes in approved projects, during the period for which approval has already been given, are not initiated without HUC review except to eliminate apparent immediate hazards to the subject.

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

*b.* Except when an expedited review is used (see para D–3), will review proposed protocols at convened meetings at which a majority of HUC members are present. For the protocol to be approved, it will receive the approval of a majority of those members present at the meetings.

*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 clinical investigations at intervals proper to the degree of risk, but not less than once per year.

*e.* 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, representative capacity, and experience such as board certifications and licenses. Information will be complete enough to describe each member's chief anticipated 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—

(1) May not reduce the safeguards or conditions if he or she approves the protocol.

(2) May require additional safeguards.

(3) May disapprove the protocol.

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

### D–3. Expedited review procedures

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

*b.* See paragraph 3–2*d* for the expedited review procedure that the HUC will follow.

### D–4. Criteria for HUC approval of clinical investigations

*a.* In evaluating risks and benefits for clinical investigations, the HUC should consider only those risks and benefits 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—

*(a)* Anticipated benefits, if any, to subjects.

*(b)* The importance of the knowledge that may reasonably be expected to result.

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

*(a)* The purpose of the investigation.

*(b)* The setting in which the clinical investigation 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) When appropriate, the plan makes adequate provision for monitoring the data collected to insure the safety of subjects.

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

*c.* Some or all of the subjects may be vulnerable to coercion or undue influence such as 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.

### D–5. 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, or

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

*b.* Suspensions or terminations of clinical investigation will include a statement of the reasons for the HUC's action. They will be reported promptly to the principal investigator and approval official.

### D–6. HUC records

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

(1) Copies of all proposals reviewed, 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 that will be in enough detail to show attendance at meetings; 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 controverted 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 for at least 10 years after completion of the clinical investigation. These records will be destroyed after 50 years. (See AR 340–18, app J.) Such records will be accessible for inspection and copying by authorized DA personnel and representatives of the Food and Drug Administration at reasonable times and in a reasonable way.

## Appendix E
## Instructions for the Completion of the Volunteer Agreement Affidavit

The principal investigator will fill in the following information in parts A and B of DA Form 5303–R and inform the subject of each entry on the form.

**E–1.** The title of the study and place where it is to be conducted.

**E–2.** The name of the principal investigator conducting the study.

**E–3.** A statement that the study involves clinical investigation. 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. A statement giving information about prior, similar, or related studies that provide the rationale for this study.

**E–4.** A description of any reasonably foreseeable risks or discomforts to the subject.

**E–5.** A description of any benefits to the subject or to others that may reasonably be expected from the study.

**E–6.** A disclosure of proper alternative procedures of courses of treatment, if any, that might be advantageous to the subject.

**E–7.** 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 protocol, a statement noting the possibility that the Food and Drug Administration may inspect the records.

**E–8.** An explanation of whom to contact for answers to pertinent questions about the study and the study subjects' rights, and whom to contact in the event of a study-related injury to the subject.

**E–9. 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.* The subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.

**E–10.** For a study involving more than minimal risk, an explanation as to whether any compensation and medical treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

**E–11.** When appropriate, one or more of the elements of information below will also be given to each subject and entered on the form.

*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.* Any additional costs to the subject that may result from participation in the study.

*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 significant new findings developed during the course of the study relating to the subject's willingness to continue to participate 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.

# Appendix F
# Expedited Review Categories

**F-1.** Collection of—

*a*. Hair and nail clippings in a nondisfiguring way.

*b*. Deciduous teeth.

*c*. Permanent teeth if patient care indicates a need for extraction.

**F-2.** Collection of—

*a*. Excreta and external secretions including sweat and uncannulated saliva.

*b*. Placenta at delivery.

*c*. Amniotic fluid at the time of rupture of the membrane before or during labor.

**F-3.** Recording of data from subjects who are 18 years of age or older, using noninvasive procedures routinely employed in the 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—

(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).

**F-4.** 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, from subjects 18 years of age or older and who are in good health and not pregnant.

**F-5.** 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.

**F-6.** Voice recordings made for research purposes such as investigations of speech defects.

**F-7.** Moderate exercise by healthy volunters.

**F-8.** Study of existing data, documents, records, pathological specimens, or diagnostic specimens.

**F-9.** Others as approved by HHS or TSG.

# Glossary

## Section I
## Abbreviations

| | |
|---|---|
| AMEDD .... | Army Medical Department |
| CFR ..... | Code of Federal Regulations |
| CIC ..... | Clinical Investigation Committee |
| CIP ..... | Clinical Investigation Program |
| DA ..... | Department of the Army |
| DCSPER ... | Deputy Chief of Staff for Personnel |
| DOD ..... | Department of Defense |
| HHS ..... | Department of Health and Human Services |
| HSC ..... | US Army Health Services Command |
| HSRRB .... | Human Subjects Research Review Board |
| HUC ..... | Human Use Committee |
| HURO ..... | Human Use Review Office |
| IDE ..... | Investigational Device Exemption |
| IND ..... | Notice of Claimed Investigational Exemption for a New Drug |
| IRB ..... | Institutional Review Board |
| MACOM ... | major Army command |
| MEDCEN .. | medical center |
| MTF ..... | medical treatment facility |
| OMA ..... | Operation and Maintenance, Army |
| POC ..... | point of contact |
| RDTE ..... | research, development, test, and evaluation |
| TSG ..... | The Surgeon General |
| UCMJ ..... | Uniform Code of Military Justice |
| USAMRDC .. | US Army Medical Research and Development Command |

## Section II
## Terms

### Associate investigator
A person who may be deeply involved in the actual execution of clinical investigations but who does not have overall primary responsibility.

### Clinical investigation
An essential component of optimum health care. Under this program, clinical investigation consists of organized scientific inquiry, both in humans and by directly related laboratory work, into clinical problems of significant concern in the necessary health care of members of the military community (including active duty personnel, dependents, and retirees) to—

*a*. Achieve continuous improvement in the quality of patient care.

*b*. Provide experience in the essential discipline achieved by those taking part in such organized inquiries; provide experience for personnel who will ultimately be teaching chiefs in military hospitals and consultants in medical facilities.

*c*. Maintain an atmosphere of inquiry because of the dynamic nature of the health sciences.

*d*. Maintain high professional standing and accreditation of advanced health programs.

### Clinical Investigation Committee (CIC)
A committee appointed by the commander to review, before HUC review, all clinical investigation protocols, to include animal and laboratory studies, for scientific adequacy, to set priorities for support, and to make recommendations.

### Consent
The legally effective agreement to take part as a human subject. The agreement may pertain to one's own participation or be in behalf of someone else's participation. Three terms associated with this meaning that distinguish between the legal validity of such agreements are subject consent, permission, and assent. These terms are defined below.

*a*. *Subject consent*. Agreement by an adult person who has autonomous legal capacity to consent to taking part as a human subject This form of consent pertains only to adults who have not lost their legal capacity to consent.

*b*. *Permission*. Agreement by a "legally authorized representative" for taking part as a human subject of another person who does not possess autonomous legal capacity to consent in his or her own behalf. A legally authorized representative is a person or judicial body authorized under applicable law to grant permission (also known as third-party consent)

*c*. *Assent*. The affirmative agreement to take part as a human subject by a person not possessing autonomous legal capacity to consent in his or her own behalf, but who is capable of understanding what is proposed and able to express an opinion as to willingness to participate. Assent is concurrence in what is proposed, but is not a substitute for subject consent because, unlike consent, assent has no legal effect.

### Epidemiological surveys
Surveys and studies of the distribution and determinants of the frequency of disease in humans. Epidemiological surveys focus on "ills" of a population rather than on persons; however, individual participation may be directly involved through the donation of blood or other body products.

### 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.

**Health care practitioner**
An individual trained to interact with patients to provide diagnostic or treatment procedures within established professional standards.

**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.

**Human subject**
*a*. A living person about whom an investigator conducting clinical investigation obtains data through interaction with the person. Both physical procedures and manipulations of the subject or the subject's environment are included. 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*. Human subjects may be classified according to their legal or mental capacities to exercise their right of choice to take part as human subjects. These classifications are as follows:

(1) *Minor*. Any person who does not qualify as an adult as defined below.

(2) *Adult*. Any person who, under the applicable laws of the jurisdiction (State) in which the clinical investigation is conducted, may consent to general medical care. (This type of consent is distinguished from consent for treatment of specific conditions such as pregnancy, drug addiction, venereal disease, and contraception.)

**Human Subjects Research Review Board (HSRRB)**
The principal body of the Office of The Surgeon General for review of clinical investigation and research activities.

**Human Use Committee (HUC)**
A body set up under any name to provide initial and continuing review of clinical investigations involving the use of human subjects. A HUC is fundamentally similar to an Institutional Review Board (IRB) (45 CFR 46) but has somewhat different authority as compared to an IRB. Within DOD, authority to approve the use of human subjects in clinical investigations is invested in commanders. Commanders act on the recommendations of validly constituted HUCs. Outside DOD, IRBs tend to be vested with this authority. Appendix D describes the membership, functions, and operations of a HUC.

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

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

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

*b*. Has become so recognized, as a result of investigations to determine its safety and effectiveness for use under such conditions.

*c*. Has not, however, otherwise been used in such investigations to a material extent or for a material time under such conditions.

**Investigational medical device**
*a*. A device that is not generally—

(1) Recognized as safe or effective.

(2) Intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease in humans.

*b*. Clinical investigation 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 investigation.

**Medical monitor**
A military or DA civilian physician who is responsible for observing human subjects during the conduct of clinical investigations.

**Minimal risk**
The risks of harm anticipated in the proposed clinical investigation are not greater, considering probability and magnitude, than—

*a*. Those ordinarily encountered in the subject's daily life, or

*b*. During the performance of routine physical or psychological examinations or tests.

**Non–US citizens**
Foreign nationals excluding, for the purposes of this regulation, personnel on active duty.

**Principal investigator**
A person, regardless of title, who is primarily responsible for the actual execution of clinical investigations.

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

*a*. The objectives of the project.

*b*. The information to be collected.

*c*. The means by which it will be collected and evaluated; an assessment of potential risk to humans; and contraindications, safety measures, and other means to be used to reduce any risk to humans.

**Schedule I controlled drug substance**
Any drug or substance by whatever official name, common or usual name, chemical name, or brand name listed in part 1308, title 21, Code of Federal Regulations.

By Order of the Secretary of the Army:

JOHN A. WICKHAM, JR.
*General, United States Army*
*Chief of Staff*

Official:

ROBERT M. JOYCE
*Major General, United States Army*
*The Adjutant General*

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## VOLUNTEER AGREEMENT AFFIDAVIT

For use of this form, see AR 40-38; the proponent agency is the Office of the Surgeon General

THIS FORM IS AFFECTED BY THE PRIVACY ACT OF 1974

1 *AUTHORITY* 10 USC 3012, 44 USC 3101 and 10 USC 1071-1087.

2. *PRINCIPAL PURPOSE* To document voluntary participation in the Clinical Investigation and Research Program SSN and home address will be used for identification and locating purpose

3 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, teaching, adjudication of claims, and for the mandatory reporting of medical condition as required by law Information may be furnished to Federal, State and local agencies

4 MANDATORY OR VOLUNTARY DISCLOSURE The furnishing of 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 - VOLUNTEER AFFIDAVIT

VOLUNTEER SUBJECTS IN APPROVED DEPARTMENT OF THE ARMY RESEARCH STUDIES

Volunteers under the provisions of 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
*(last, first, middle)*

*full capacity to consent and having attained my* _____ birthday, do hereby volunteer to participate in

_____
*(research study)*

_____

under direction of _____ conducted at _____
*(name of institution)*

*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 on study-related injury I may contact

_____

*at* _____
*(name and address of hospital & phone number (include area code))*

I understand that I may at any time during the course of this study revoke my consent and withdraw from the study without further penalty or loss of benefits however, I 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 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 E, AR 40-38 or AR 70-25 )

(CONTINUE ON REVERSE)

PART B - TO BE COMPLETED BY INVESTIGATOR *(cont'd)*

| SIGNATURE OF VOLUNTEER | DATE SIGNED | SIGNATURE OF LEGAL GUARDIAN *(If volunteer is a minor)* |
|---|---|---|
| PERMANENT ADDRESS OF VOLUNTEER | TYPED OR PRINTED NAME AND SIGNATURE OF *WITNESS* | DATE SIGNED |

*Reverse of DA FORM 6303 R Apr 84*