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1. Transmitted is a revision to Department of Veterans Affairs, Veterans Health Administration Manual M-3, "Research and Development in Medicine," Part I, "General," Chapter 9, "Requirements for the Protection of Human Subjects." Brackets have not been used to indicate changes.

2. Principal changes

a. This chapter has been retitled to reflect the provisions of the Common Rule for the Protection of Human Subjects, codified at 38 CFR (Code of Federal Regulations) 16.

b. Paragraphs 9.02, 9.03 and 9.04 have been revised.

3. Filing Instructions

Remove pages	Insert pages
iii through viii	iii through ix
9-i through 9-9	9-i through 9-16
	9A-1 through 9C-3

4. RESCISSIONS: M-3, part I, chapter 9, dated March 5, 1985; VHA Circular 10-89-034, dated March 31, 1989, and Supp. No. 1; VHA Circular 10-90-044, dated April 13, 1990, and Supp. No. 1; VHA Circular 10-90-046, dated April 16, 1990, and Supp. No. 1; VHA Circular 10-90-052, dated May 1, 1990, and Supp. No. 1; VHA Circular 10-90-069, dated June 19, 1990, and Supp. No. 1.

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FOREWORD

VA (Department of Veterans Affairs) Veterans Health Administration Manual M-3, "Research and Development in Medicine," Part I, "General," April 27, 1982, has been completely rewritten to incorporate all policy and procedural changes and additions in the administration of research and development since that date. Parts II, III, and IV have also been completely rewritten to provide a convenient, readable set of documents for clear communication and effective administration of research and development. Similar reissuances are planned at 2-year intervals in the future.

The Research and Development Manual covers all three Research and Development Services and is organized as follows:

- Part I General
- Part II Medical Research Program
- Part III Health Services Research and Development
Program
- Part IV Rehabilitation Research and Development Program

The provisions of this manual apply to all medical, rehabilitation and health services research conducted in VA medical centers, both locally and centrally reviewed.

RESCISSIONS

The following material is rescinded:

1. COMPLETE RESCISSIONS

a. Manuals

M-3, part I, chapter 9, dated March 5, 1985, and change 3 dated January 6, 1988

M-3, part I, chapter 12, dated January 31, 1989

b. Interim Issues

II 10-68-2

II 10-68-3

II 10-69-14

II 10-81-44

c. Circulars

10-84-75

10-84-198 and Supplement No. 1

10-85-128

10-87-27 and Supplement No. 1

10-87-53 and Supplement No. 1

10-87-110 and Supplement No. 1

10-89-034 and Supplement No. 1

10-89-131 and Supplement No. 1

10-90-044 and Supplement No. 1

10-90-046 and Supplement No. 1

10-90-052 and Supplement No. 1

10-90-069 and Supplement No. 1

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CHAPTER 9. REQUIREMENTS FOR THE PROTECTION OF HUMAN
SUBJECTS IN RESEARCH

9.01 INTRODUCTION

The recent publication of the Federal Policy for the Protection of Human Subjects (56 FR 28001-32, June 18, 1991) meets a widely recognized need for uniformity among Federal departments and agencies in ensuring protection of the rights and welfare of individuals involved as subjects of research under Federal auspices. This policy is a result of several years effort to formulate a uniform policy that would eliminate unnecessary regulation and promote increased understanding and ease of compliance by institutions, organizations, and individuals who conduct Federally supported or regulated research involving human subjects.

9.02 PURPOSE

This chapter implements 38 CFR (Code of Federal Regulations) 16. The policies and procedures set forth in this chapter supersede all previous VA (Department of Veterans Affairs) directives related to the protection of human subjects in research.

9.03 POLICY

a. VA is one of the 16 departments and agencies that have agreed to follow the Federal Policy for the Protection of Human Subjects, effective August 19, 1991. This policy is incorporated in 38 CFR 16.

b. With the exception of categories listed in appendix 9A, the provisions of this chapter apply to all research involving human subjects conducted completely or partially in VA facilities, including research funded from extra-VA sources and research conducted without direct funding.

c. Investigators receiving support from such Federal agencies as the National Institutes of Health must meet the human subjects requirements of the funding source. However, since these agencies are also regulated by the Federal Policy for the Protection of Human Subjects, their human subjects requirements will not differ importantly from the requirements expressed in this chapter.

9.04 DEFINITIONS

The following terms, defined in 38 CFR 16.12, are defined more specifically for the purposes of this chapter

a. Legally Authorized Representative. A legally authorized representative means an individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research. For the purposes of this chapter, a "legally authorized representative" includes not only persons appointed as health care agents under DPAHC (Durable Powers of Attorney for Health Care), court appointed guardians of the person but also next- of-kin in the following order of priority:

(1) Spouse.

(2) Adult child (18 years of age or older).

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(3) Parent.

(4) Adult sibling (18 years of age or older).

b. Human Subject. The definition of human subject provided in the Federal Policy is expanded to include investigators, technicians, and other assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled.

c. IRB (institutional review board). IRB is defined in the Federal Policy as an institutional review board established in accord with and for the purposes expressed in this policy. For the purposes of this chapter, the Subcommittee on Human Studies of the Research and Development Committee constitutes an IRB. Therefore, IRB will be used to refer to either the Subcommittee on Human Studies and any affiliated university IRB that may service a VA facility.

9.05 AUTHORITY

a. Statutory provisions for protection of VA patient rights: 38 U.S.C. (United States Code) Sections 7331 through 7334.

b. VA regulations pertaining to protection of patient rights: 38 CFR Sections 17.34 and 17.34a.

c. VA regulations pertaining to rights and welfare of patients participating in research: 38 CFR 16 (Federal Policy for the Protection of Human Subjects).

d. DHHS (Department of Health and Human Services) regulations pertaining to rights and welfare of patients participating in research supported by DHHS: 45 CFR 46.

e. FDA (Food and Drug Administration) regulations pertaining to rights and welfare of patients participating in research involving investigational drugs and devices: 21 CFR parts 50 and 56.

9.06 RESEARCH EXEMPT FROM THE PROVISIONS OF THIS CHAPTER

a. Exempt categories. Research activities in which the only involvement of human subjects will be in one or more of the minimal risk categories listed in appendix 9A of this chapter are exempt from the requirements of this chapter. An IRB must approve the exempt status.

b. Determination of exemption. An investigator wishing to have a research proposal exempted from IRB review shall present a request in writing, along with the research proposal, to the R&D (Research and Development) Committee. The request will be justified by showing that the proposed research falls into one or more of the categories listed in appendix 9A.

c. Documentation of Research and Development Committee action. The Research and Development Committee or its designee shall review all requests for exemption in a timely manner, record its decision along with the basis of the decision, and communicate the decision in writing to the investigator.

9.07 MEDICAL CENTER RESPONSIBILITIES

- a. Establishing an IRB. Every VA medical center shall either:
- (1) Have or establish an IRB (Subcommittee on Human Studies).

(2) Arrange for securing the services of a Subcommittee on Human Studies from another VA facility, including the Eastern and Western R&D Offices.

(3) Arrange for securing the services of an IRB established by an affiliated medical or dental school:

(a) If the medical center chooses to use the services of an affiliated university IRB, VA interests will be adequately represented, usually by the inclusion of at least one VA employee with scientific expertise on the IRB.

(b) An IRB established by an affiliated medical or dental school must agree to comply with the provisions of 38 CFR 16.

(c) When VA utilizes an IRB established by an affiliated medical or dental school, the informed consent forms that will be used by prospective veteran-subjects must include a statement in compliance with paragraph 2a(12) of appendix 9C.

b. Operating an IRB. Every VA medical center will provide (if needed) meeting space and sufficient staff to support the IRB's review and record keeping duties. The authorities and responsibilities of IRB's are described in paragraph 9.09.

9.08 IRB COMPOSITION

a. Number and Qualification of Members

(1) Each IRB will have at least five members, with varying backgrounds to promote complete and adequate review of research activities commonly conducted by the medical center.

(a) The IRB will be sufficiently qualified through the experience and expertise of its members, and the diversity of the members, including consideration of:

1. Race.
2. Gender.
3. Cultural backgrounds.
4. Sensitivity to community issues and/or community attitudes.

(b) The IRB will:

1. Promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects.

2. Possess the professional competence necessary to review specific research activities.

(2) The IRB, to be able to ascertain the acceptability of proposed research in terms of medical center commitments and policies, applicable law, and standards of professional conduct and practice, will, therefore, include persons knowledgeable in these areas.

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b. Group Heterogeneity

(1) Every nondiscriminatory effort will be made to ensure that no IRB consists

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entirely of men or entirely of women, including the medical center's consideration of qualified persons of both sexes, so long as no selection is made to the IRB on the basis of gender.

(2) No IRB may consist entirely of members of one profession.

c. Scientific/nonscientific Members

(1) Each IRB will include at least one member whose primary concerns:

(a) Are in scientific areas.

(b) Are in nonscientific areas.

(2) These members will be selected primarily to reflect the values of the community with respect to the rights and welfare of human research subjects.

(3) To serve as part of the IRB, it is recommended that members of the community be considered, such as:

(a) Clergypersons.

(b) Attorneys.

(c) Representatives of legally recognized veterans organizations.

(d) Practicing physicians.

d. Non-VA Members. Each IRB will include at least one member who is not otherwise affiliated with the medical center and who is not part of the immediate family of a person who is affiliated with the medical center.

e. Conflict of Interest. No IRB may have a member participate in the IRB's initial or continuing review of any project in which the member has a conflicting interest, except to provide information requested by the IRB.

f. Ad Hoc Members. An IRB may, in its discretion, invite individuals with competence in special areas to assist in the review of issues which require expertise beyond or in addition to that available on the IRB. These individuals may not vote with the IRB.

9.09 IRB AUTHORITY AND RESPONSIBILITIES

a. IRB Authority and Review Criteria. An IRB will review and have authority to approve, require modifications in (to secure approval), or disapprove all research activities covered by this chapter. In order to approve research governed by this policy the IRB will determine that all of the following requirements are satisfied:

(1) Minimization of Risks. Risks to subjects are minimized:

(a) By using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and

(b) Whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

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(2) Reasonable Risk/benefit Ratio. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result.

(a) In evaluating risks and benefits, the IRB should consider only those risks and benefits that may result from the research (as distinguished from risks and benefits of therapy subjects would receive even if not participating in the research).

(b) The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.

(3) Equitable Selection of Subjects. Selection of subjects is equitable. In making this assessment, the IRB should take into account the purposes of the research and the setting in which the research will be conducted and should be particularly cognizant of the special problems of research involving vulnerable populations, such as:

- (a) Children;
- (b) Prisoners;
- (c) Pregnant women;
- (d) Mentally disabled persons; or
- (e) Economically or educationally disadvantaged persons.

(4) Securing Informed Consent. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by appendix 9C.

(5) Documenting Informed Consent. Informed consent will be appropriately documented, in accordance with and to the extent required by paragraph 9.11b.

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

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

(8) Protection of Vulnerable Subjects. IRB will ensure that additional safeguards have been included in the study to protect the welfare of subjects likely to be vulnerable to coercion or undue influence, such as:

- (a) Children;
- (b) Prisoners;
- (c) Pregnant women;

(d) Mentally disabled persons; or

(e) Economically or educationally disadvantaged persons.

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b. Notifying Investigators

(1) An IRB will notify investigators and the R&D Committee in writing of its decision to approve or disapprove the proposed research activity, or of modifications required to secure IRB approval of the research activity.

(2) If the IRB decides to disapprove a research activity, it will include in its written notification a statement of the reasons for its decision and give the investigator an opportunity to respond in person or in writing.

c. Maintaining Written Procedures for Operations. An IRB will follow written procedures:

(1) For conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the R&D Committee.

(2) For determining which projects require review more often than annually and which projects need verification from sources other than the investigators that no material changes have occurred since previous IRB review; and

(3) For ensuring prompt reporting to the IRB of proposed changes in a research activity, and for ensuring that such changes in approved research, during the period for which IRB approval has already been given, may not be initiated without IRB review and approval except when necessary to eliminate apparent immediate hazard to the subject.

d. Maintaining Written Procedures for Reporting Noncompliance. An IRB will prescribe written procedures for ensuring prompt reporting by investigators to the IRB, appropriate medical center officials, and appropriate VA Central Office officials for:

(1) Any unanticipated problems involving risks to human subjects or others;

(2) Any instance of serious or continuing noncompliance with this policy or the requirements or determinations of the IRB; and

(3) Suspension or termination of IRB approval.

e. Obtaining a Quorum for Review. Except when an expedited review procedure is used (see par. 9.10), the IRB will review proposed research at convened meetings at which a majority of the members are present, including at least one member whose primary concerns are in nonscientific areas. In order for the research to be approved, it will receive the approval of a majority of those members present at the meeting.

f. Monitoring Ongoing Projects. An IRB shall conduct continuing review of research covered by this policy at intervals appropriate to the degree of risk, but not less than once per year, and will have authority to observe or have a third party observe the consent process and its research.

g. Monitoring IRB Records

(1) Necessary Documentation. A medical center, or when appropriate an IRB, shall prepare and maintain adequate documentation of IRB activities, including the following:

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(a) Proposals and evaluations. Copies of all research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved sample consent documents, progress reports submitted by investigators, and reports of injuries to subjects.

(b) Minutes. Minutes of IRB meetings which will be in sufficient detail to show:

1. Attendance at the meetings;
2. Actions taken by the IRB;
3. The vote on these actions including the number of members voting for, against, and abstaining;
4. The basis for requiring changes in or disapproving research; and
5. A written summary of the discussion of controverted issues and their resolution.

(c) Ongoing review. Records of continuing review activities.

(d) Correspondence. Copies of all correspondence between the IRB and the investigator.

(e) Membership list

1. A list of IRB members identified sufficiently to describe each member's chief anticipated contributions to IRB deliberations, such as:

- a. Name.
- b. Earned degrees.
- c. Representative capacity.
- d. Indications of experience such as board certifications, licenses, etc.

2. Any employment or other relationship between each member and the medical center will be noted, for example:

- a. Full-time employee.
- b. Part-time employee.
- c. Member of governing panel or board.
- d. Paid or unpaid consultant.

(f) Procedures. Written procedures for conducting reviews, monitoring ongoing projects, and identifying and reporting problems with regard to compliance with the provisions of this chapter.

(g) New findings. Statements of significant new findings provided to subjects, as required by paragraph 2b(5) of appendix 9C.

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(2) Record retention

(a) The records required will be retained in accordance with VHA's Records Control Schedule 10-1.

(b) All records will be accessible for inspection and copying by authorized representatives of VA at reasonable times and in a reasonable manner.

9.10 IRB RESPONSIBILITIES AND EXPEDITED REVIEW

a. Circumstances for Expedited Review. An IRB may use the expedited review procedure to review either or both of the following:

(1) Eligible categories. Any of the categories of research appearing in appendix 9B and found by the R&D Committee to involve no more than minimal risk.

(2) Approval of minor changes. Minor changes in previously approved research during the period (of 1 year or less) for which approval is authorized.

b. Procedures. Under an expedited review procedure, the review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB.

(1) In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research.

(2) A research activity may be disapproved only after review in accordance with the non-expedited procedure.

c. Record Keeping. Each IRB which uses an expedited review procedure will adopt a method for keeping all members advised of research proposals which have been approved under the procedure.

9.11 INVESTIGATOR RESPONSIBILITIES

a. Obtaining Informed Consent. Investigators wishing to involve human beings as subjects in research covered by this chapter will obtain legally effective informed consent of the subject or the subject's legally authorized representative. The basic elements of informed consent are listed in appendix 9C.

b. Documenting Informed Consent

(1) Written consent form. Except as provided in subparagraph 2b(3), informed consent will be documented by the use of a written consent form and signed by the subject or the subject's legally authorized representative. The original signed consent form must remain in the patient's chart and copies must be retained in the experimental/research file under conditions of confidentiality.

(2) Two alternatives. Except as provided in subparagraph 2b(3), the consent form may be either of the following:

(a) Written consent document. A written consent document that embodies the elements of informed consent required by appendix 9C. NOTE: VA Form 10-1086, VA Research Consent Form, shall be used to meet these requirements. VA Form 10-1086,

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may be read to the subject or the subject's legally authorized representative, but in any event, the investigator will give either the subject or the representative adequate opportunity to read it before it is signed; or

(b) Written consent document (short form). A short form written consent document stating that the elements of informed consent required by appendix 9C have been presented orally to the subject's legally authorized representative. When this method is used, there will be a witness to the oral presentation. This process includes the following:

1. The IRB will approve a written summary of what is to be said to the subject or the representative.

2. Only the short form itself is to be signed by the subject or the representative.

3. The witness will sign both the short form and a copy of the summary, and the person actually obtaining consent will sign a copy of the summary.

4. A copy of the summary will be given to the subject or the representative, in addition to a copy of the short form.

(3) Waiver of requirement. An IRB may waive the requirement for the investigator to obtain a signed consent form for some or all subjects if it finds either:

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

(b) That the research presents no more than minimal risk of harm to subjects and involves no procedures for which written consent is normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the investigator to provide subjects with a written statement regarding research. (Approved by the Office of Management and Budget under Control Number 9999-0020.)

9.12 RESEARCH ON HUMAN SUBJECTS WITH SURROGATE CONSENT

a. Policy. Under appropriate conditions, investigators may obtain informed consent from the legally authorized representative of patients (surrogate consent).

(1) Such consent may be obtained not only from health care agent appointed by the patient in a DPAHC or similar document, court-appointed guardians of the person but also from next-of-kin in the following order of priority:

(a) Spouse.

(b) Adult child (18 years of age or older).

(c) Parent.

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(d) Adult sibling (18 years of age or older).

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(2) Such consent may be requested and accepted only when the prospective research participant is incompetent as determined by two VA physicians, after appropriate medical evaluation and there is little or no likelihood that the patient will regain competence within a reasonable period of time, or as established by a legal determination.

(3) This policy is designed to protect patients from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to patients who are incompetent (e.g., a study of treatment options for comatose patients can only be done with incompetent subjects).

b. Criteria for IRB Approval. Before incompetent persons may be considered for participation in any VA research, the IRB must find that the proposed research meets all of the following conditions:

(1) Only incompetent patients suitable. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or subjects. Incompetent persons must not be subjects in research simply because they are readily available.

(2) Favorable risk/benefit ratio. The proposed research entails no significant risks, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people will not be subjects of research which imposes a risk of injury unless that research is intended to benefit the subject and the probability of benefit is greater than the probability of harm.

(3) Voluntary participation. Although incompetent to provide informed consent, some patients may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

(4) Well-informed representatives. Procedures have been devised to assure that participants' representatives are well-informed regarding their roles and obligations to protect incompetent subjects. Health care agents (appointed under DPAHC's) and next-of-kin or guardians must be given descriptions of both proposed research studies and the obligations of patients' representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interests.

c. IRB Procedure. The IRB shall make a determination in writing of each of the criteria listed in 9.12b. If these criteria are met, the IRB may approve the inclusion of incompetent subjects in research projects on the basis of informed consent from authorized representatives or next-of-kin as described in 9.12 a(1).

9.13 PAYMENT OF SUBJECTS

a. Policy. VA policy prohibits paying patients to participate in research when the research is an integral part of a patient's medical care and when it makes no special demands on the patient beyond those of medical care. Payment

may be permitted, with prior approval of the IRB, in the following circumstances:

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(1) No direct subject benefit. When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated, non-VA institutions is to pay patients in this situation.

(2) Others being paid. In multi-institution studies, where patients at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.

(3) Comparable situations. In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers is appropriate.

b. Procedure. Prospective investigators who wish to pay research subjects shall indicate in their proposal the justification for such payment with reference to the criteria listed and, in addition, shall:

(1) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;

(2) State the terms of the subject participation agreement and the amount of payment in the informed consent form; and

(3) Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure on the veteran patient to volunteer for the research study.

c. Committees. R&D Committees and IRBs shall review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of the policies in this chapter.

d. Research Offices. The research office shall ensure that IRB-approved payment to subjects is made from "medical and prosthetic research funds" (including General Post funds).

9.14 USE OF VA RECORDS FOR RESEARCH AND DEVELOPMENT

a. VA personnel are bound by all legal and ethical requirements to protect the rights of R&D subjects, including the confidentiality of information that can be identified with a person.

b. VA personnel may obtain and use for approved R&D purposes medical, technical, and administrative records from other VA facilities as well as those available locally. Requests for records from other facilities must be approved by the R&D Committee and the facility Director before being submitted to the appropriate R&D service director in VA Central Office.

c. Persons not employed by the VA can only be given access to medical and other VA records for R&D purposes within the legal restrictions imposed by such laws as the Privacy Act of 1974, and 38 U.S.C. Requests for such use must be submitted to the AsCMD/R&D (Associate Chief Medical Director for Research and Development) in VA Central Office at least 60 days before access is desired. Requests for information filed pursuant to the Freedom of Information Act ordinarily require a response within 10 working days. Agency

implementing guidelines and policy must be adhered to when such requests are received so that a timely reply can be made.

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9.15 INVESTIGATIONAL DRUGS IN RESEARCH WITH HUMAN SUBJECTS

a. The use of drugs in research must be carried out in a responsible manner.

(1) The use of controlled substances, such as narcotics and barbiturates, requires even more stringent monitoring.

(2) The storage and security procedures for drugs used in research shall follow all Federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations. Such procedures apply as well to drugs used for animal studies in basic research.

b. An investigational drug for clinical use is one for which a sponsor has filed an IND (Investigational New Drug) application with, and which has been approved by, the FDA.

(1) The use of an investigational drug in clinical research must be conducted according to a protocol approved by the Subcommittee on Human Studies and the R&D Committee of the VA medical center.

(2) The principal investigator of an investigational drug study is responsible for securing the informed written consent of each patient subject on VA Form 10-1086 in compliance with the procedures described in paragraph 9.11. The original of the signed informed consent form, VA Form 10-1086, will be filed in the patient's medical record.

(3) A VA Form 10-9012, Investigational Drug Information Record, must be completed by the principal investigator and monitored by the R&D Committee.

(a) The original of this form will be kept on file in Pharmacy Service as a part of the study protocol.

(b) A copy for each patient, with the appropriate patient identification, will be filed in the patient's medical record.

(4) The principal investigator is also responsible for furnishing a copy of the approved protocol to the Chief, Pharmacy Service, of the VA medical center involved in the study.

c. When the Subcommittee on Human Studies and the R&D Committee approve the research study employing an investigational drug, VA Form 10-1223, Report of Subcommittee on Human Studies, will be prepared with copies forwarded to the investigator and to the Chief, Pharmacy Service. The original will be placed in the protocol file in the medical center's Research Office.

(1) The principal investigator will be responsible for obtaining the investigational drug from the manufacturer and delivering it or having it delivered, with proper identification, in accordance with FDA regulations (21 CFR 312) to the custody of the Chief, Pharmacy Service.

(2) The investigational drug will be ordered from Pharmacy Service on a properly completed VA Form 10-2577f, Prescription Form, signed by an authorized prescriber registered with the Chief, Pharmacy Service.

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d. The date contained in VA Form 10-9012 will serve as a protocol abstract and a copy of this form will be forwarded by Pharmacy Service for inclusion in the individual medical record each time a patient is entered in the study.

e. Prior to dispensing an investigational drug, Pharmacy Service will verify that an informed consent form, VA Form 10-1086, has been signed. Such verification shall be made by review of the consent form in the Pharmacy Service.

(1) The principal investigator must send Pharmacy Service a copy of this form for each patient entered in the study.

(2) Each time the drug is issued to laboratory personnel for use in laboratory studies, a written authorization signed by the principal investigator is required.

(3) The principal investigator must inform the Chief, Pharmacy Service, and the R&D Committee when a study involving investigational drugs has been terminated and must direct in writing the disposition of any remaining drug. M-2, part VII, "Pharmacy Service," was published for the compliance of all concerned; chapter 6 provides information on "Research and Investigational Drugs."

f. In the late stages of a drug's investigation, and in certain limited situations, the drug may be used as a humanitarian act outside the regular protocol in individual cases.

(1) In such cases, patients must become participants in the research protocol (21 CFR 50.3(g)) and an emergency life-threatening situation must necessitate the use of the drug (21 CFR 50.23(a)).

(2) Use of an investigational drug as a humanitarian act requires:

(a) Separate authorization from the Chief Medical Director for each patient outside the protocol (M-2, pt. I, ch. 3, par. 3.03b);

(b) The filing of VA Form 10-9012 with the Chief, Pharmacy Service; and

(c) A report to the facility Human Studies Subcommittee within 5 days (21 CFR 56.104(c)).

NOTE: Further details concerning such use of an investigational drug appear in M-2, part I, chapter 3.

g. In the case of a VA Cooperative Study employing investigational drugs, the Cooperative Studies Program Clinical Research Pharmacy at the VA Medical Center, Albuquerque, NM, will prepare the Investigational Drug Information Record which will list the name, address, and Social Security number of the study chairperson as it appears on VA Form 10-1436, Research and Development Information System Project Data Sheet.

(1) After the Investigational Drug Information Record has been signed by the Participating Investigator, one copy will be sent to the Chief, Pharmacy Service, of the Participating Investigator's VA medical center and one copy

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will be included in the protocol maintained in the medical center's Research Office.

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(2) The Chief, Pharmacy Service, of the participating investigator's VA medical center will also receive a copy of FDA Form 1571, Investigational New Drug Application (IND), a copy of the IND letter from the FDA, and FDA Form 1572, Statement of the Investigator, for the respective participating investigator from the Cooperative Studies Program Clinical Research Pharmacy.

(3) A copy of the "Report of Subcommittee on Human Studies" indicating the approval of the study must also be forwarded from the local Research Office to the appropriate Cooperative Studies Program Coordinating Center assisting the study.

h. The Cooperative Studies Program Clinical Research Pharmacy will be responsible for obtaining the investigational drug and for distributing it to the Chief, Pharmacy Service, of each authorized participating VA medical center.

i. The Pharmacy Service of each participating VA medical center will maintain records on the investigational drug dispensed and will make arrangements in accordance with applicable VA and FDA regulations for disposition of the unused drug when its participation in the cooperative study is terminated.

j. When a new drug or device is considered investigational, the full range of side effects, adverse reactions, and complications associated with it are unknown. When an investigational new drug or device is to be used with human subjects, the manufacturer develops a detailed statement or investigational protocol of:

(1) How the testing is to be accomplished;

(2) What the human volunteer is to be told about the nature of the research;

(2) Benefits from participation in the research;

(3) The risks and complications which may arise from the research, and

(4) What are the alternatives to participation.

k. Indemnification Agreements. Because, as with all research, there may be a risk of injury or adverse reaction, the manufacturer will sometimes offer to indemnify the VA medical center at which the testing is to be conducted and the VA investigator who conducts the testing in order to induce their cooperation and participation.

(1) The General Counsel's opinion is that the indemnification agreements that are commonly used in such situations usually do little more than restate the common law rule of indemnity. Rarely does the manufacturer's indemnification shield the investigator or participating VA medical center from liability or serve to act as an insurer.

(2) Without some compelling reason, the VA will not enter into these types of indemnification agreements.

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(3) If there is a compelling reason, execution of the agreement requires the express approval of the General Counsel.

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(a) Such agreements and their supporting documents must be forwarded to the General Counsel's Office in VA Central Office for review and approval prior to their execution.

(b) Supporting documentation should include, but not be limited to:

1. Local VA Medical Center Research and Development Committee approval;
2. Human Studies Subcommittee approval;
3. The protocol which both bodies reviewed;
4. Data supplied by the manufacturer; and
5. Other materials necessary for the General Counsel to render a determination.

9.16 VA/FDA MEMORANDUM OF UNDERSTANDING

a. There is a Memorandum of Understanding between the VA and the FDA. It was negotiated in order to facilitate communication and encourage effective cooperation between the agencies in the area of clinical research with investigational new drugs, including biological and medical devices, and to accommodate FDA site visits to Human Studies Subcommittees at VA facilities.

b. In 1977, in response to a congressional directive, FDA developed a program to assure the quality of biological research data intended to support the approval of new drugs, biological, and medical devices. The main objectives of this program are to:

- (1) Assure protection of human subjects participating in the research;
- (2) Assess, through audit procedures, whether data submitted to FDA in specific studies are valid; and
- (3) Determine whether clinical investigators and Human Studies Subcommittees or IRBs (Institutional Review Boards) are complying with the regulations. NOTE: FDA has applied the same standards of performance to Federal institutions and Government employees that it has applied to private industry.

c. The following procedures have been adopted by VA and FDA:

(1) FDA will notify the medical center Director at the VA medical center whenever a clinical investigator or Human Studies Subcommittee IRB is to be inspected so that suitable arrangements for the inspection may be made.

(2) VA will facilitate access to administrative records and patient medical records associated with any investigational new drug and device research subject to FDA regulations and will also provide copies of those records upon the official request of an FDA investigator. Access to these records is authorized under the Privacy Act of 1974 (5 U.S.C. 552a(b)(3) and (7)) and the VA confidentiality statutes (38 U.S.C. 5701(b)(3), 5705(b)(1)(C), and 7332(b)(2)(B)).

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(3) VA will review internal guidelines for clinical research with
investigational new drugs and medical devices to assure that VA guidelines are
consistent with FDA

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regulations for the conduct and reporting of investigational studies. Such review will also be conducted with regard to VA Human Studies Subcommittee IRB procedures.

(4) FDA will promptly advise the VA, through the liaison officer, of any violative findings resulting from investigations into the performance of clinical investigators or Human Studies Subcommittees IRBs associated with the VA.

(5) Following the inspection, FDA will forward to the VA liaison officer and the VA medical center Director a copy of any post-inspection correspondence to the clinical investigator or Human Studies Subcommittee IRB Chairperson resulting from the inspection. Upon request, FDA will send to the VA liaison officer copies of specific inspection reports and reviews pertaining to VA clinical investigators and Human Studies Subcommittees IRB inspections.

(6) In accordance with 21 CFR 20.85, VA agrees to maintain the confidentiality of any information from an FDA open investigatory file provided to VA under this agreement.

(7) FDA recognizes that disclosure of information obtained from VA records is subject to restrictions under the Privacy Act of 1974 and the VA confidentiality statutes. FDA personnel having access to drug, alcohol, and sickle cell anemia treatment records subject to the confidentiality provisions of 38 U.S.C. 7332 are not permitted to redisclose patient identities, directly or indirectly, in any manner in any report or audit documents which are created in accordance with this agreement. Violations of 38 U.S.C. 7332 may result in the imposition of fines and other adverse consequences.

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CATEGORIES OF EXEMPT RESEARCH

Research activities in which the only involvement of human subjects will be in one or more of the following categories, are exempt from review by VA (Department of Veterans Affairs) Subcommittees on Human Studies and other IRB's (Institutional Review Board) used by VA investigators:

1. Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as:

a. Research on regular and special education instructional strategies, or

b. Research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.

2. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement) survey procedures, interview procedures or observation of public behavior, unless:

a. Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and

b. Any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability or reputation.

3. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior that is not exempt under paragraph 2, if:

a. The human subjects are elected or appointed public officials or candidates for public office, or

b. Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.

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

5. Research and demonstration projects which are conducted by or subject to the approval of department or agency heads, and which are designed to study, evaluate, or otherwise examine:

a. Public benefit or service programs.

b. Procedures for obtaining benefits or services under those programs.

c. Possible changes in or alternatives to those programs or procedures.

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d. Possible changes in methods or levels or payment for benefits or services under those programs. NOTE: This exemption was not originally intended for research conducted in a hospital setting. Although included in the exemption list, VA policy requires that prior approval of its use be approved by the Associate Chief Medical Director for Research and Development (12).

6. Taste and food quality evaluation and consumer acceptance studies:

a. If wholesome foods without chemical additives are consumed, or

b. If a food is consumed that contains a food ingredient at or below the level of safety and for a use found to be safe, or agricultural chemical or environmental contaminant at or below a level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

ACTIVITIES APPROPRIATE FOR EXPEDITED REVIEW

NOTE: Research that requires any invasive procedure (with the exception of the procedures described in paragraph 4) is regarded as involving more than minimal risk and hence is not appropriate for expedited review.

NOTE: Expedited review may be used for minor changes in previously approved research during the period for which approval is authorized.

Activities appropriate for expedited review are:

1. Collection of:
 - a. Hair and nail clippings, in a nondisfiguring manner;
 - b. Deciduous teeth; and
 - c. Permanent teeth if patient care indicates a need for extraction.
2. Collection of excreta and external secretions including:
 - a. Sweat;
 - b. Uncannulated saliva;
 - c. Placenta removed at delivery; and
 - d. Amniotic fluid at the time of rupture of the membrane prior to or during labor.
3. Recording of data from subjects 18 years of age or older using noninvasive procedures routinely employed in clinical practice. This 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. It also includes such procedures as:
 - a. Weighing;
 - b. Testing sensory acuity;
 - c. Electrocardiography;
 - d. Electroencephalography;
 - e. Thermography;
 - f. Detection of naturally occurring radioactivity;
 - g. Diagnostic echography; and
 - h. Electroretinography.

NOTE: It does not include exposure to electromagnetic radiation outside the visible range (for example, X-rays, microwaves).

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4. Collection of blood samples by venipuncture, in amounts not exceeding 450 milliliters in an 8-week period and no more than two times per week, from subjects 18 years of age or older and who are in good health and not pregnant.
5. Collection of both supra- and subgingival dental plaque and calculus, provided the procedure is not more invasive than routine prophylactic scaling of teeth and the process is accomplished in accordance with accepted prophylactic techniques.
6. Voice recordings made for research purposes such as investigations of speech defects.
7. Moderate exercise by healthy volunteers.
8. The study of existing:
 - a. Data;
 - b. Documents;
 - c. Records;
 - d. Pathological specimens; or
 - e. Diagnostic specimens.
9. Research on individual or group behavior or characteristics of individuals, such as:
 - a. Studies on perception;
 - b. Cognition;
 - c. Game theory; or
 - d. Test development, where the investigator does not manipulate subjects' behavior and the research will not involve stress to subjects.
10. Research on drugs or devices for which an investigational new drug exemption or an investigational device exemption is not required.

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PROCEDURES FOR OBTAINING INFORMED CONSENT

1. No investigator may involve a human being as a subject in research unless the investigator has obtained the legally effective informed consent of the subject or the subject's legally authorized representative. NOTE: See paragraph 9.06 for exemptions.

a. An investigator will seek such consent only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence.

b. The information that is given to the subject or the representative will be in language understandable to the subject or the representative.

c. No informed consent, whether oral or written, may include any exculpatory language through which the subject or the representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the sponsor, the institution or its agents from liability for negligence.

2. Basic elements for informed consent

a. Except as provided in subparagraphs 2c and 2d, in seeking informed consent the following information will be provided to each subject:

(1) A statement that the study involves research.

(2) An explanation of the purposes of the research and the expected duration of the subject's participation.

(3) A description of the procedures to be followed.

(4) Identification of any procedures which are experimental.

(5) A description of any reasonably foreseeable risks or discomforts to the subject.

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

NOTE: An explanation will be provided as to whether compensation and/or medical treatment is available if injury occurs and, if so, what it consists of or where further information may be obtained.

(7) A disclosure of appropriate alternative procedures of courses of treatment, if any, that might be advantageous to the subject.

(8) A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.

(9) For research involving more than minimal risk, an explanation as to whether any compensation and an explanation as to whether any medical

treatments are available if injury occurs and, if so, what they consist of, or where further information may be obtained.

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

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

(12) A statement that a veteran-subject will not be required to pay for treatment received as a subject in a VA research program. Investigators should note; however, that veterans in the "discretionary work load" category are subject to making a copayment if so indicated by a means test (M-1, pt. 1, ch. 4, par. 4.30). The veteran subject will receive medical care and treatment for injuries suffered as a result of participating in a VA research program, in accordance with Federal law.

b. Additional elements of informed consent. When appropriate, one or more of the following elements of information will also be provided to each subject:

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

(2) Anticipated circumstances under which the subject's participation may be terminated by the investigator without regard to the subject's consent.

(3) Any additional costs to the subject that may result from participation in the research, consistent with the Federal laws concerning veterans' eligibility for medical care and treatment.

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

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

(6) The approximate number of subjects involved in the study.

(7) A verbatim statement:

"I authorize the use of my bodily fluids, substances, or tissues.";

NOTE: Required if the researcher believes that bodily fluids, substances or tissues of a research subject could be part of or lead to the development of a commercially valuable product.

(8) A statement regarding any payment the subject is to receive.

(9) A verbatim statement:

"I have been informed that because this study involves articles regulated by the FDA (Food and Drug Administration), the FDA may choose to inspect research

identifying me as a subject of this investigation." NOTE: Required if research involves a drug with an IND (Notice of Claimed Investigational Exemption for a New Drug) or a medical device with an IDE (Investigational Device Exemption).

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c. An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent provided the IRB finds and documents that:

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

(a) Public benefit of service programs;

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

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

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

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

d. An IRB may approve a consent procedure which does not include, or which alters, some or all of the elements of informed consent set forth in this section, or waive the requirements to obtain informed consent provided the IRB finds and documents that:

(1) The research involves no more than minimal risk to the subjects;

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

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

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

e. The informed consent requirements stated are not intended to preempt any applicable federal, state, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

f. Nothing in this policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law. (Approved by the Office of Management and Budget under Control Number 9999-0020.)