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Federal Regulation: The Protection of Human Subjects in Research

Veteran Health Administration (VHA) Mission

The mission of the Veterans Healthcare System is to serve the needs of America's veterans by providing primary care, specialized care, and related medical and social support services. To accomplish this mission, VHA needs to be a comprehensive, integrated healthcare system that provides excellence in health care value, excellence in service as defined by its customers, and excellence in education and research, and needs to be an organization characterized by exceptional accountability and by being an employer of choice.

VHA Vision

Healthcare Value begins with VA. The new Veterans Healthcare System supports innovation, empowerment, productivity, accountability and continuous improvement. Working together, we provide a continuum of high quality health care in a convenient, responsive, caring manner — and at a reasonable cost.

VHA Goal

Goal is to provide excellence in patient care, veterans' benefits and customer satisfaction.

Statistic

Of the 25 million veterans currently alive, nearly three of every four served during a war or an official period of hostility. About a quarter of the nation's population --

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approximately 70 million people -- are potentially eligible for VA benefits and services because they are veterans, family members or survivors of veterans.

The total veteran population is 25 millions including 8,055,000 Vietnam era veterans, Gulf war era veterans 4,378,000, World War II veterans 3,526,000, while Korean conflict veterans 3, 257,000, World war I veterans are too few in number to estimate reliably. Veterans serving only in peacetime numbered 6,231,000, about one-in-four veterans.

Age

As September 30, 2005, the median age of all veterans was 59.3 years. Veterans under age 45 constituted 20 % of the total, while those aged 45-64 represented 41 %, and those 65 or older were 38 % of the total.

Sex:

Female veterans numbered 1, 712,000 million, representing 7 % of the total veteran population. Roughly one-in-five resident U.S males 18 years of age or older is a veteran.

Office of Research and Development (ORD)

ORD is the office within VA Central Office responsible for the overall policy, planning, coordination, and direction of research activities within VHA.

1. The [Program for Research Integrity Development & Education \(PRIDE\)](#) is responsible for all policy development and guidance, and all training and education in human research protection throughout the VA. The work of developing policies, guidance, education and training will be carried out by PRIDE centers such as the Guidance and Policy Center (GUIDE) and the Center on Advice and Compliance Help (COACH).

2. Office of Research Oversight (ORO)

ORO is the primary VHA office for advising the Under Secretary for Health on all matters regarding compliance and oversight of research in the protection of human subjects, animal welfare, and research safety. ORO oversees investigations of allegations of research misconduct.

Human Research Protection Program (HRPP)

An HRPP is a comprehensive system to ensure the protection of human subjects participating in research. The HRPP consists of a variety of individuals and committees such as: the Medical Center Director, Associate Chief of Staff (ACOS) for Research and Development (R&D), the Administrative Officer (AO) for R&D, compliance officers, etc., the R&D Committee, the IRB, other committees or subcommittees addressing human subjects protection (e.g., Bio-safety, Radiation Safety, Radioactive Drug Research, Conflict of Interest), investigators, IRB staff, research staff, health and safety staff (e.g., Bio-safety

Officer, Radiation Safety Officer) and research pharmacy staff. The objective of this system is to assist the institution in meeting ethical principles and regulatory requirements for the protection of human subjects in research.

VA Regulation

Introduction

The Department of veterans Affairs (VA) is one of the seventeen Federal Departments and agencies that have agreed to follow the Federal Policy for the Protection of Human Subjects (Common Rule), effective June 18, 1991 (56 Federal Register (FR) 28001). This policy is incorporated in Title 38 Code of Federal Regulations (CFR) Part 16. This Veterans Health Administration (VHA) Handbook defines the procedures implementing 38 CFR Part 16. The VA is guided by the basic ethical principles (respect for persons, beneficence, and justice) regarding all research involving humans as subjects, as set forth in the Belmont report "Ethical Principles and Guidelines for the Protection of Human Subjects of Research," regardless of who conducts the research or the source of support. Investigators receiving support from other Federal agencies, such as the National Institutes of Health (NIH), must meet requirements for the protection of human subjects of the funding source in addition to those of VA. If FDA-regulated test articles are used, the FDA regulations apply regardless of funding source (21 CFR Parts 11, 50, 54, 56, 312, 314, 600, 812, and 814). It is imperative that human research subjects receive the highest level of protection possible and that any questions or any legal or ethical ambiguities always be resolved in favor of the human research subject.

VA Authority

1. Statutory provisions for protection of **VA patient rights** Title 38 United States Code (U.S.C.) Sections 501, 7331, and 7334.
2. VA regulations pertaining to protection of patient rights; 38 CFR 17.33a and 17.34.
3. VA regulations pertaining to **rights and welfare of human subjects** participating in research: 38 CFR 16 (Federal Policy for the Protection of Human Subjects).
4. VA regulations pertaining to research related injuries: 38 CFR 17.85.
5. Statutes and regulations pertaining to the **release of patient information**: 5 U.S.C. § 552a; 38 U.S.C. §§ 5701a, 7332; 45 C.F.R. Parts 160-164.
6. VA regulations pertaining to **hospital care for research** purposes and outpatient care for research purposes: 38 CFR 17.45, 17.92.
7. Department of Health and Human Services (**DHHS**) regulations **pertaining to rights and welfare** of human subjects participating in research supported by DHHS: 45 CFR 46.

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8. Food and Drug Administration (FDA) regulations pertaining to **rights and welfare** of human subjects participating in research involving investigational drugs and devices: 21 CFR Parts 11, 50, 54, 56, 312, 360.1, 600, 812, and 814.

9. **Nuclear Regulatory Commission (NRC) regulations** pertaining to medical use of By-product material and protection of human subjects: 10 CFR Parts 20 (Standards for Protection Against Radiation) and 35 (Medical Use of Byproduct Material).

10. **VA confidentiality** of medical quality assurance records statute: 38 U.S.C. 5705.

11. An **Assurance** is also called an Assurance of Compliance, or a Federal-wide Assurance (FWA). It is a written commitment by an institution to protect human subjects participating in research. Under federal regulations, any institution conducting or engaged in federally supported research involving human subjects must obtain an Assurance in accordance with 38 CFR 16.103. NOTE: All research conducted under VA auspices is considered to be Federally-supported. This requirement also applies to any collaborating "performance site" Institutions. Under 38 CFR 16.102(f), an institution is engaged in human subject research whenever its employees or agents: intervene or interact with living individuals for research purposes; or obtain, release, or access individually-identifiable private information for research purposes. Assurances are filed through the VA Office of Research Oversight (ORO) with the Department of Health and Human Services (DHHS) Office for Human Research Protections (OHRP). The FWA replaces previous types of OHRP and VA assurances.

12. **Exempt Research.** Exempt research is research determined by the Institutional Review Board (IRB) to involve human subjects only in one or more of certain minimal risk categories (38 CFR 16.101(b)).

Approval of Exempt Category

Investigators must submit the proposed research and the request for exemption to the IRB. The IRB Chair, or an IRB member designated by the Chair, must review all requests for exemption in a timely manner, make a determination based on 38 CFR 16.101, and record the decision. The decision must be communicated in writing to the investigator and the IRB. Documentation must include the specific categories justifying the exemption. Projects that are exempt from IRB review must be reviewed by the R&D Committee prior to initiation and then they must be included in its annual review of research projects.

Research activities in which the only involvement of human subjects will be in one or more of the following categories may be exempt from review by the Institutional Review Board (IRB) unless otherwise required by the IRB. Guidance on research that may be exempt, but includes vulnerable populations such as children or prisoners may be found in Appendix D. The exempt status must be approved by the IRB Chair or an IRB member designated by the Chair. When research is determined to be exempt the IRB and the Research and Development (R&D) Committee must be notified and the exemption documented in the IRB records.

NOTE: Research involving prisoners or focused on pregnant women may not be exempt. There are restrictions on the use of exemption for research involving children.

The exempt categories, as stated in Title 38 Code of Federal Regulations (CFR)16.101(b), are: Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as: Research on regular and special education instructional strategies, or Research on the effectiveness of or the comparison

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among instructional techniques, curricula, or classroom management methods. Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior unless: Information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and Any disclosure of the 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. NOTE: The Department of Veterans Affairs (VA) also includes loss of insurability in this category. 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 preceding subparagraph 2b, if the subjects are elected or appointed public officials or candidates for public office, or Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information must be maintained throughout the course of research and thereafter. Research involving the use 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, either directly or through identifiers linked to the subjects. Research and demonstration projects that are conducted by, or subject to, the approval of department or agency heads, and that are designed to study, evaluate, or otherwise examine public benefit or service programs, procedures for obtaining benefits or services under such programs, possible changes in or alternatives to such programs, and possible changes in methods or levels of payment for benefits or services under such programs.

NOTE: The determination of exempt status for these research and demonstration projects must be made by the Under Secretary for Health on behalf of the Secretary of Veterans Affairs, after consultation with Office of Research and Development, the Office of Research Oversight, the Office of General Counsel, and other experts, as appropriate. Taste and food quality evaluation and consumer acceptance studies as defined in 38 CFR 16.101(b).

13. EXPEDITED REVIEW

Expedited research is research determined by the IRB to present no more than minimal risk to human subjects and involve only procedures in certain specific categories. Minor changes to previously approved research during the period for which approval is authorized may also be approved through the expedited process (38 CFR 16.110(b)). An expedited review procedure consists of a review of research involving human subjects by the IRB chairperson or by one or more experienced reviewers designated by the chairperson from among members of the IRB in accordance with the requirements set forth in 38 CFR 16.110.

Research activities may be reviewed by an expedited review process, unless otherwise required by the Institutional Review Board (IRB). (Authority: Title 45 Code of Federal Regulations (CFR) 46.110, 38 CFR 16.110, and 21 CFR 56.110.) The following is extracted from 63 FR 60364-60367, November 9, 1998, "Protection of Human Subjects: Categories of Research That May Be Reviewed by the Institutional Review Board (IRB) Through an Expedited Review Procedure."

1. Research that presents **no more than minimal risk to human subjects**.
2. The expedited review process may not be used when identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability; or be

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damaging to the subject's financial standing, employability, insurability, and/or reputation; or be stigmatizing, unless reasonable and appropriate protections are implemented so that risks related to invasion of privacy and breach of confidentiality are minimal.

3. The expedited review process may not be used for classified research involving human subjects.

4. IRBs are reminded that the standard requirements for informed consent (or its waiver, alteration, or exception) apply to expedited review.

5. The research categories appropriate for **expedited review pertain to both initial and continuing IRB review.**

6. Research Categories

A. Clinical studies of drugs and medical devices, only when one of the following conditions is met.

(i) Research on drugs for which an investigational new drug application (21 CFR Part 312) is not required. NOTE: Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with the use of the product is not eligible for expedited review.

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

B. Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:

(1) From healthy, non-pregnant adults who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 milliliters (ml) in an 8-week period and collection may not occur more frequently than 2 times per week; or

(2) From other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than two times per week. NOTE: Children are defined in the HHS regulations as "persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted" see 45 CFR 46.402(a). Source: 63 Federal Register (FR) 60364-60367, November 9, 1998. VA does not conduct research-involving children as subjects unless a waiver has been obtained from the CRADO (see App. D).

C. Prospective collection of biological specimens for research purposes by noninvasive means. Examples are as follows:

(1) Hair and nail clippings in a non-disfiguring manner.

(2) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.

(3) Permanent teeth if routine patient care indicates a need for extraction.

(4) Excreta and external secretions (including sweat).

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(5) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.

(6) Placenta removed at delivery.

(7) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.

(8) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.

(9) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.

(10) Sputum collected after saline mist nebulization.

D. Collection of data through non-invasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. NOTE: For VA approved research, the term x-rays as used in this Appendix means ionizing radiation as defined in paragraph 3 of this Handbook. Where medical devices are employed, they must be cleared and/or approved for marketing. NOTE: Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications. Examples of procedures eligible for expedited review are:

(1) Physical sensors that are applied either to the surface of the body or at a distance, and do not involve input of significant amounts of energy into the subject, or an invasion of the subject's privacy.

(2) Weighing or testing sensory acuity.

(3) Magnetic resonance imaging.

(4) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, doppler blood flow, and echocardiography.

(5) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.

E. Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes (such as medical treatment or diagnosis). NOTE: Some research in this category may be exempt from the VA regulations for the protection of human subjects (38 CFR 16.101(b)(4)). This listing refers only to research that is not exempt.

F. Collection of data from voice, video, digital, or image recordings made for research purposes.

G. Research on individual or group characteristics or behavior (including, but not limited to, research on: perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior), or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance

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methodologies. NOTE: Some research in this category may be exempt from the VA regulations for the protection of human subject (38 CFR 16.101(b)(2) and (b)(3)). This listing refers only to research that is not exempt.

H. Continuing review of research previously approved by the convened IRB as follows:

- (1) Research in which the enrollment of new subjects is permanently closed; all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or
- (2) Research in which no subjects have been enrolled and no additional risks have been identified; or
- (3) Research in which the remaining research activities are limited to data analysis.

I. Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories (listed in subpars. 2b through 2h of this App.) do not apply, but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

J. Minor changes in previously approved research during the period for which approval is authorized. If approved, the continuing review date does not change, but remains the same as determined at the most recent review. NOTE: If the change involves bio-safety or ionizing radiation, the appropriate committee must be consulted prior to approving the change; the consultation with these committees must be documented in the IRB file.

Human Subject

A human subject is a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual or through identifiable private information (38 CFR 16.102(f)). The definition provided in the Common Rule includes investigators, technicians, and others assisting investigators, when they serve in a "subject" role by being observed, manipulated, or sampled. As required by 38 CFR 16.102(f) an intervention includes all physical procedures by which data are gathered and all physical, psychological, or environmental manipulations that are performed for research purposes.

NOTE: The FDA definition of human subject differs according to the applicable regulation. See 21 CFR 812.3(p), 21 CFR 50.3(g), 312.3(b,) and 56.102(e).

Investigational Device

As defined by the FDA, an investigational device is a device that is the object of a clinical study designed to evaluate the safety or effectiveness of the device (21 CFR 812.3(g)). Investigational devices include transitional devices (21 CFR 812.3(r)) that are objects of investigations. However, for the purposes of this VHA Handbook, an investigational device may be an approved device that is being studied for an unapproved use or efficacy.

Investigational Drug

An investigational drug is a drug or biological drug that is used in a clinical investigation. The FDA considers the term "Investigational New Drug (IND)" synonymous with investigational drug (21 CFR 312.3). However, for purposes of this VHA Handbook, an

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Investigational Drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.

Investigational Device Exemption (IDE)

An IDE is an FDA-approval of the application for an exemption that permits an un-marketed device to be shipped for the purpose of doing research on the device. NOTE: See 21 CFR 812.1 and 812.2 for scope and applicability.

Investigational New Drug (IND)

An IND used to refer to either an investigational new drug application or to a new drug that is used in clinical investigations. IND is synonymous with "Notice of Claimed Investigational Exemption for a New Drug."

NOTE: See 21 CFR 312.2(a)-(b) for applicability and exemptions.

IRB

An IRB is a board established in accordance with and for the purposes expressed in the Common Rule (38 CFR 16.102(g).) Within VHA, an IRB was formerly known as the Subcommittee on Human Studies. At VA medical centers, the IRB is a subcommittee of the R&D Committee.

Quorum

A quorum is defined as a majority of the voting members as listed on the IRB membership. In the case of the IRB, a quorum must include at least one member whose primary concerns are in non-scientific areas. At meetings of the IRB, a quorum must be established and maintained for the deliberation and vote on all matters requiring a vote.

Research

Research is defined as the testing of concepts by the scientific method of formulating a hypothesis or research question, systematically collecting and recording relevant data, and interpreting the results in terms of the hypothesis or question. The Common Rule (38 CFR 16) defines research as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. NOTE: The FDA definition of research differs according to the applicable regulations; see 21 CFR 812.3(h), 21 CFR 50.3(c), 21 CFR 56.102(c), and 21 CFR 312.3(b).

Research Records

Research records consist of IRB records as well as case histories (also referred to as investigator's research records) or any data gathered for research purposes.

IRB Records

IRB records include but are not limited to: all minutes of IRB meetings, a copy of all proposals reviewed including all amendments, investigator brochures, any supplemental information including recruitment and informational materials, consent forms, information submitted for continuing review, all correspondence, and IRB membership with a resume for each member.

Case History

A case history is a record of all observations and other data pertinent to the investigation on each research subject. An investigator is required to prepare and maintain adequate and accurate case histories. Case histories include the case report forms and supporting data including signed and dated consent forms, any medical records including, but are not limited to: progress notes of the physician, the individual's hospital chart(s), and nurses' notes. The case history for each individual must document that informed consent was obtained prior to participation in the study.

Test Article

For purposes of this VHA Handbook, a test article is a drug, device, or other article including a biological product used in clinical investigations involving human subjects or their specimens.

VA-approved Research

VA-approved research is research that has been approved by the VA R&D Committee.

IRB COMPOSITION

The IRB is responsible for ascertaining the acceptability of proposed research in terms of medical center commitments and policies, applicable law, validity of study design as it relates to risks and benefits, sensitivity to community standards and attitudes, as well as standards of professional conduct and practice. NOTE: The IRB's composition plays a pivotal role in its ability to fulfill its role. Each IRB, whether that of the VA or the affiliate, must have at least five members with varied backgrounds to promote complete and adequate review of research activities commonly conducted by the institutions (VA and affiliate) for which it reviews research. The IRB members must be sufficiently qualified to review the research through their experience, expertise, and diversity, including consideration of race, gender, cultural backgrounds, and sensitivity to community issues and/or attitudes. The IRB must promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; and possess the professional competence necessary to review specific research activities (38 CFR 16.107(a)). In the appointment of IRB members, equal consideration must be given to qualified persons of both genders. No appointment to the IRB will be made solely on the basis of gender. Every non-discriminatory effort will be made to ensure that the IRB membership does not consist entirely of men or entirely of women (38 CFR 16.107(b)). No IRB may consist entirely of members of one profession (38 CFR 16.107(b)). Each IRB must include at least one member whose primary expertise is in scientific areas and at least one member whose primary expertise is in non-scientific areas (38 CFR 16.107(c)). These members are to be selected primarily to reflect the values of the research community and the community from which the research subjects are drawn with respect to the rights and welfare of human research subjects. Each IRB must include at least one member who is not otherwise affiliated with the VA medical center and who is not part of the immediate family of a person who is affiliated with the medical center (38 CFR 16.107(d)). Members of the community such as clergy persons, teachers, attorneys, veterans, or representatives of legally-recognized veterans organizations, and practicing physicians need to be considered for appointments to the IRB. No IRB may have a member participate in the review of any project in which the member has a conflict of interest, except to provide information requested by the IRB (38 CFR 107(e)). An IRB may, at its discretion, invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on the IRB. These

individuals may not vote with the IRB (38 CFR 16.107(f)). The R&D administration officials including, but not limited to the ACOS for R&D and the AO for R&D, may not serve as voting members of the IRB. The ACOS for R&D, AO for R&D and/or a Research Compliance Officer may serve as non-voting members and must be sensitive to the occurrence or appearance of conflict of interest. Alternate members may be formally appointed to the IRB. The IRB's written procedures must describe the appointment and function of alternate members, and the IRB roster must identify the primary member(s) for whom each alternate member may substitute. The alternate member's qualifications must be comparable to those of the primary member to be replaced. When an alternate member replaces the primary member, the alternate member must receive and review the same material that the primary member received. In addition, the IRB minutes must document instances in which an alternate member replaces a primary member. IRB members and R&D Committee members need to forward names for consideration for new IRB members to the Medical Center Director. Other VA personnel may submit names to the IRB or R&D committee to be forwarded to the Medical Center Director for consideration. The Medical Center Director must officially appoint members in writing. The VA representatives to affiliate IRBs must be appointed by the Medical Center Director for a period of 3 years and may be re-appointed indefinitely.

IRB RESPONSIBILITIES AND AUTHORITY

Minimization of Risks

Risks, both physical and non-physical, to human subjects are minimized by: using procedures that are consistent with sound research design; that do not unnecessarily expose subjects to risk; and, whenever appropriate, using procedures already being performed on the subjects for diagnostic or treatment purposes. NOTE: Consultation with subject matter experts and review by such committees or subcommittees as Biosafety, Radiation Safety and/or Radioactive Drug Research may be necessary to ensure risks to human subjects are minimized.

Reasonable Risk Benefit Ratio

Risks, both physical and non-physical, to human subjects are reasonable in relation to any anticipated benefits (the risk benefit ratio) to subjects, and the importance of the knowledge that may reasonably be expected to result. Validity of research design must be taken into consideration in determining the risk benefit ratio. In evaluating risks and benefits, the IRB needs to consider only those risks and benefits that may result from the research, as distinguished from risks and benefits the subjects would receive even if not participating in the research (38 CFR 16.111(a)(2)). The IRB must consider the risks and benefits related to both biomedical (including genetic) research and non-biomedical research.

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

Equitable Selection of Subjects

In assessing whether selection of subjects is equitable, the IRB needs to take into account the purposes of the research and the research setting. The IRB needs to be particularly cognizant of the special problems of research involving vulnerable populations such as: children, prisoners, pregnant women, mentally disabled persons or persons with impaired decision-making capacity, and economically or educationally disadvantaged persons.

Review and Approval of the Informed Consent Form

The IRB is responsible for the review and approval of the informed consent form prepared by the investigator; VA Form 10-1086, Research Consent Form, must be used. The wording on VA Form 10-1086 must contain all of the required elements and meet all other requirements outlined in Appendix C. If the wording of the informed consent has been initially prepared by an entity (e.g., a pharmaceutical company or a cooperative study group including National Cancer Institute (NCI) groups) other than the VA PI, the IRB needs to ensure that the wording of the consent meets all the requirements of, or has been reviewed by, the appropriate VA committees and subcommittees such as the Subcommittee on Research Safety and the Radiation Safety Committee. IRB approval of the wording of the consent must be documented through the use of a stamp on each page of the VA Form 10-1086 that indicates the date of the most recent IRB approval of the document. If the consent form is amended during the protocol approval period, the form must bear the approval date of the amendment rather than the date of the approved protocol.

The IRB needs to ensure that the required language for a valid authorization to release health information (Health Insurance Portability and Accountability Act (HIPAA) Authorization) is included in the informed consent document. The IRB may waive the requirement for an authorization or may alter the form or content of the authorization only in accordance with and as permitted by the HIPAA Privacy Rule (45 CFR 164.508). Such actions and the justification for them must be fully documented in the minutes of the IRB meeting where the action was taken or reported (if approved by expedited review). NOTE: See VHA Handbook 1605.1, regarding Privacy.

Securing Informed Consent and Documentation of the Informed Consent Process

Informed consent must be sought from each prospective subject or the subject's authorized representative, in accordance with, and to the extent required by Appendix C. A person knowledgeable about the consenting process and the research to be conducted must obtain the informed consent. If someone other than the investigator conducts the interview and obtains consent, the investigator needs to formally delegate this responsibility and the person so delegated must have received appropriate training to perform this activity. It is the responsibility of the IRB to ensure that the informed consent process is appropriately documented.

Monitoring On-going Projects

An IRB must conduct continuing review of research at intervals appropriate to the degree of risk, but not less than once per year. The IRB has the authority to observe or have a third party observe the consent process.

Monitoring Safety

The research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects (38 CFR 16.111(a)(6)). The plan may include establishing a Data Safety and Monitoring Board (DSMB) or a Data Monitoring Committee (DMC) as required by DHHS or FDA policy, and a plan for reporting DSMB or DMC findings to the IRB. The IRB must review the data and safety-monitoring plan in the protocol developed by the investigator. In addition, for studies that do not have or are not required to have a DSMB or DMC and are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, the IRB needs to carefully review the data and safety-monitoring plan. The plan needs to include procedures for reporting AEs.

Amendments

All amendments to the project or changes in the informed consent must be reviewed and approved by the IRB prior to initiating the changes, except when necessary to eliminate immediate hazard(s) to the subject(s). If the amendment addresses an issue related to bio-safety or radiation safety, the appropriate committee or subcommittee must first approve the amendment.

Privacy and Confidentiality

Adequate provisions must be taken to protect the privacy of subjects and to maintain the confidentiality of individually-identifiable data. Such provisions must consider the requirements of Standards for Privacy of Individually-Identifiable Health Information (HIPAA Privacy Rule), 45 CFR Parts 160 and 164, and other laws regarding protection and use of veterans' information, including Privacy Act of 1974, 5 U.S.C. 552a; VA Claims Confidentiality Statute, 38 U.S.C. 5701; Confidentiality of Drug Abuse, Alcoholism and Alcohol Abuse, Infection with Human Immunodeficiency Virus (HIV), and Sickle Cell Anemia Medical Records, 38 USC 7332; and Confidentiality of Healthcare Quality Assurance Review Records, 38 USC 5705.

Documentation, as required by 45 CFR 164(i)(2), indicating the approval of a waiver or alteration of the HIPAA Authorization.

Protection of Vulnerable Subjects

The IRB must ensure that additional safeguards have been included in each study to protect the welfare of vulnerable subjects. The IRB needs to consider inclusion, as regular or ad hoc members, of one or more individuals who are knowledgeable about and experienced in working with these vulnerable subjects.

Conflict of Interest

The IRB must ensure that steps to manage, reduce or eliminate potential or real conflicts of interest (financial, role (investigator/patient relationships), and/or institutional) have been taken. All VA investigators must comply with VHA policies and procedures regarding conflict of interest.

Investigator's Educational Requirements and Certification

The IRB must determine that the PI and all other investigators of the proposed research activity have met all current educational requirements for the protection of human research subjects as mandated by the facility's Assurance, VA ORD, funding institutions, and applicable OHRP requirements. The IRB must also determine that the investigator(s) is qualified through education, training, and experience to conduct the research.

Initiation of Research Projects

All proposed research involving human subjects must be reviewed and approved by the IRB and the R&D Committee prior to initiation of the research project. The date of continuing review will be based on the date of IRB approval. NOTE: The R&D committee may not approve the research until all other appropriate subcommittees of the R&D committee and other committees (e.g., Bio-safety, Radiation Safety) have reviewed the research.

Communication with Investigators

An IRB must notify the PI and the R&D Committee in writing of its decision to approve or disapprove a proposed research activity, or of modifications required to secure IRB approval. An IRB-approved research activity may be disapproved by the R&D Committee, the medical Center Director, or the ORD. If a research activity is disapproved by the IRB, the decision cannot be overruled by the R&D Committee, or any higher authority. The R&D Committee and higher authority may strengthen requirements and/or conditions, or add other modifications to secure R&D approval or approval by a higher authority. Previously approved research proposals and/or consent forms must be re-approved by the IRB before initiating the changes or modifications. Along with written notification of approval, a copy of the approved consent form containing the stamped approval and date of the approval on each sheet must be sent to the investigator and must be filed in the protocol files maintained by the IRB or the facility research office. If the IRB disapproves a research activity, it must include a statement of the reasons for its decision in its written notification to the investigator and give the investigator an opportunity to respond in person or in writing. If the IRB conducts or receives a report of any internal audits of an investigator's research files, the IRB must notify the investigator of any findings that require changes.

Maintaining Written Procedures for Operations

The IRB must establish written procedures for, but not limited to: Conducting its initial and continuing review of research and for reporting its findings and actions to the investigator and the R&D Committee. Determining which projects require review more often than annually and which projects need verification from sources, other than the investigator, that no material changes have occurred since previous IRB review. Ensuring that investigators promptly report proposed changes in a research activity including amendments to the protocol, or the consent form, to the IRB, and ensuring that such changes in approved research are not initiated without the IRB's review and approval, except when necessary to eliminate apparent immediate hazard to the subject. Reporting promptly to the IRB regarding non-compliance by study personnel. Notifying medical center officials and VA Central Office of any AEs that cause harm or risk of harm to human subjects or groups as required by this Handbook, other VA policies, or Federal regulations; any instance of serious or continuing noncompliance with this Handbook or the requirements of determinations of the IRB; and suspension or termination of IRB approval.

Record Retention

1. The required records, including the investigator's research records, must be retained for a minimum of 5 years after the completion of the study and in accordance with VHA's Records Control Schedule (**RCS 10-1**), applicable FDA and DHHS regulations, or as required by outside sponsors.
2. All records must be accessible for inspection and copying by authorized representatives of VA, OHRP, FDA and other authorized entities at reasonable times and in a reasonable manner.
3. Records are the property and the responsibility of the local research office. The medical center must designate where the records will be maintained and/or stored.
4. Complete (non-redacted) minutes, whether from the VA or affiliate IRB reviewing VA research, must be submitted to the R&D Committee and maintained in the facility research

office. The R&D Committee must review and act upon all IRB minutes regardless whether the IRB is established at the medical center or at the affiliate university.

RESEARCH INVOLVING HUMAN SUBJECTS WITH SURROGATE CONSENT

Under appropriate conditions, investigators may obtain consent from the legally authorized representative of a subject (surrogate consent). This policy is designed to protect human subjects from exploitation and harm and, at the same time, make it possible to conduct essential research on problems that are unique to persons who are incompetent, or who have an impaired decision-making capacity (e.g., a study of treatment options for comatose persons can only be done with incompetent subjects). Such consent may be obtained from: a health care agent appointed by the person in a DPAHC or similar document; court-appointed guardians of the person, or from next-of-kin in the following order of priority, unless otherwise specified by applicable state law: spouse, adult child (18 years or older), parent, adult sibling (18 years of age or older), grandparent, or adult grandchild (18 years of age or older). NOTE: The preceding list contains the only surrogate entities who are allowed to provide consent for research purposes. Such consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person's medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements in subparagraphs 11a(3)(a-d), or as established by a legal determination. NOTE: The consent requirements described in this Handbook are not intended to preempt any applicable Federal, State or local laws that require additional information to be disclosed for the informed consent to be legally effective in accordance with **38 CFR 16.116(e)**.

(a) The practitioner, in consultation with the chief of service, or COS, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.

(b) Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.

(c) Disclosures required by this Handbook to be made to the subject by the investigator must be made to the subject's surrogate.

(d) If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

PAYMENT FOR SUBJECTS

a. The VA policy prohibits paying human subjects to participate in research when the research is integrated with a patient's medical care and when it makes no special demands on the patient beyond those of usual medical care. Payment may be permitted, with IRB approval, in the following circumstances:

(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 subjects in this situation.

(2) Others Being Paid. In multi-institutional studies, when human subjects 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 subjects is appropriate.

(4) Transportation Expenses. When transportation expenses are incurred by the subject

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that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

b. Prospective investigators who wish to pay research subjects must in their proposal:

- (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 or influence on the perspective research subjects to volunteer for, or to continue to participate in, the research study; and that the payments do not constitute (or appear to constitute) coercion to participate in, or continue to participate in, the research study.

c. The IRB and R&D Committee must review all proposals for payment of subjects to ensure conformity with VA policies.

d. The facility research office is responsible for ensuring that IRB-approved payment to subjects is made from a VA approved funding source for research activities.

USE OF VA RECORDS FOR RESEARCH AND DEVELOPMENT

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

b. Obtaining and using medical, technical, and administrative records from other VA facilities or VA databases (national, regional, or subject specific) for R&D purposes must be in compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information (45 CFR Parts 160 and 164). Obtaining and disclosing individually-identifiable patient records must be in compliance with all applicable and confidential statues and regulations including those discussed in subparagraph 7a(7).

c. Persons not employed by VA can be given access to medical and other VA records for R&D purposes only 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 CRADO in VA Central Office at least 60 days before access is desired. Requests for information filed pursuant to the Freedom of Information Act ordinarily requires a response within 10 working days. VA guidelines and policy must be followed when making such requests to allow for a timely reply. This does not apply to those individuals having access for the purpose of monitoring the research. Obtaining and using the records must be in compliance with all VHA regulations and with the Standards for Privacy of Individually-Identifiable Health Information (45 CFR Parts 160 and 164).

INVESTIGATIONAL DRUGS IN RESEARCH WITH HUMAN SUBJECTS

Use of investigational drugs must be conducted according to FDA IND regulations, 21 CFR Part 312, and other applicable FDA and VA regulations.

a. The use of drugs in research must be carried out in a responsible manner. The storage and security procedures for drugs used in research must follow all Federal rules, regulations, and laws regarding controls and safety that pertain in ordinary clinical situations.

b. An investigational drug for clinical research use is one for which the PI or a sponsor has filed an IND application (21 CFR Part 312). Pursuant to these regulations an IND application goes into effect 30 days after FDA receives the application (unless the investigations described in the IND application are subject to clinical hold), or on earlier notification by FDA that the clinical investigation may begin (21 CFR 312.40). For purposes of this

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Handbook, an investigational drug is also defined as an approved drug that is being studied for an unapproved or approved use in a controlled, randomized, or blinded clinical trial.

c. The PI is responsible for informing Pharmacy Service that IRB and R&D Committee approval has been obtained. This must be through the use of VA Form 10-1223, Report of Subcommittee on Human Studies, to be sent to Pharmacy Service. VA Form 10-9012, Investigational Drug Information Record, or superseding forms must be provided to the pharmacy by the PI as required in VHA Manual M-2, Part VII, Chapter 6, or superseding policy document. In addition a signed copy of VA Form 10-1086, must be sent to Pharmacy Service to document each subject's consent to participate in the study.

d. The PI must inform the Chief, Pharmacy Service, and the R&D Committee when a study involving investigational drugs has been terminated.

e. All applicable requirements in M-2, Part VII, Chapter 6, or superseding policy document must be met.

f. FDA regulations provide for exceptions to the general requirements for obtaining informed consent under two specific situations:

(1) When the human subject is confronted by a life-threatening situation necessitating the use of the drug, when a legally effective informed consent cannot be obtained from the subject, when time is not sufficient to obtain consent from the subject's legally-authorized representative, and when there is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the life of the subject (21 CFR. § 50.23(a)).

(2) If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject and time is not sufficient to obtain the independent determination required in 21 CFR § 50.23(a) in advance of using the drug (21 CFR § 50.23(b)).

g. FDA regulations (21 CFR 312.34 and 312.35) address the treatment use of an investigational drug (not approved for marketing, but under clinical investigation for a serious or immediately life-threatening disease condition) in patients for whom no comparable or satisfactory alternative drug or other therapy is available. Use of the investigational drug for this purpose must meet all applicable FDA requirements.

h. FDA regulations at 21 CFR 312.34, 312.35, and 312.36 address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23). All applicable regulations must be met including those at 21 CFR Parts 50 and 56, and 21 CFR 312.34 and 312.35.

i. Emergency Exemption from Prospective IRB Approval. FDA defines emergency use as the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval. If all conditions described in 21 CFR 56.102(d) exist then the emergency exemption from prospective IRB approval found at 21 CFR 56.104(c) may be utilized. Informed consent is required unless the conditions for exemption are met. The IRB must be notified within 5 working days when an emergency exemption is used. Any subsequent use of the test article at the institution is subject to IRB review.

INVESTIGATIONAL DEVICES IN RESEARCH WITH HUMAN SUBJECTS

Use of an investigational device in a clinical trial to obtain safety and effectiveness data must be conducted according to FDA's IDE regulations, 21 CFR Part 812, other applicable FDA regulations, and applicable VHA regulations.

a. The IRB reviewing investigational medical device protocols must have written procedures for: conducting the reviews, determining if the device represents a "significant risk," and reporting findings to the investigator.

b. If the study of the device is not exempt (21 CFR 812.2(c)), the device must be characterized as "significant risk" (SR) or "non-significant risk" (NSR) by the IRB. The IRB must determine and document if the device represents SR or NSR. NOTE: See FDA Information Sheets, 1998, for lists of SR and NSR devices or the FDA web site (www.FDA.gov).

c. SR device studies must be conducted in accordance with the full IDE requirements (21 CFR Part 812). Pursuant to these regulations, an investigation may begin 30 days after FDA receives the application (unless FDA provides notification that the investigation may not begin), or after the FDA approves, by order, an IDE for the investigation (21 CFR 812.30). In addition, the investigator must have approvals from the IRB and R&D committee. The FDA considers all SR studies to be greater than minimal risk. NOTE: The IRB needs to verify the existence of the IDE when applicable.

d. NSR device studies do not require submission of an IDE application, but must be conducted in accordance with the "abbreviated requirements" of the IDE regulations (21 CFR 812.2(b)). NOTE: NSR devices may represent greater than minimal risk depending upon the research study.

e. Unless otherwise notified by the FDA, a NSR study is considered to have an approved IDE if all abbreviated requirements are fulfilled.

f. The IRB must review the research in accordance with these requirements and needs to use the same criteria it would use in considering approval of any research involving an FDA-regulated product (21 CFR 56.111).

g. NSR device studies may commence immediately following IRB and R&D Committee approval, if no changes are required by either committee.

h. The VA facility must have procedures for receipt, control, custody, and dispensing of the investigational devices.

i. The PI is responsible for compliance with all applicable FDA regulations.

j. Emergency use of unapproved devices must follow FDA guidance.

PARTICIPATION OF NON-VETERANS AS RESEARCH SUBJECTS

a. Non-veterans may be entered into VA-approved research studies only when there are insufficient veterans available to complete the study in accordance with 38 CFR 17.45 and 38 CFR 17.92.

b. All regulations pertaining to the participation of veterans as research subjects including requirements for indemnification in case of research-related injury pertain to non-veteran subjects enrolled in VA-approved research.