

# Investigator Handbook for Research Involving Human Subjects



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## Introduction

The George E. Wahlen VAMC Salt Lake City HCS (VASLCHCS) Investigator Handbook for Research Involving Human Subjects is a reference for Investigators and Study Coordinators. This Handbook details the policies and procedures governing human subjects' research and the requirements for submitting research proposals for review and approval by the Research and Development Committee (R&D).

Investigators and Study Coordinators may also reference the University of Utah (UU) Institutional Review Board (IRB) website at [www.utah.edu/irb](http://www.utah.edu/irb), which provides additional guidance for submitting research to the UU IRB for review and approval.

For additional information and/or reference materials, Investigators and Study Coordinators are always welcome to contact the VASLCHCS Research Service located at 500 Foothill Drive, Building 2, Second Floor. Hours of operation are 7:00 am - 4:30 pm, Monday through Friday. Point of Contact is Lorna S. Kamber, Research Compliance Officer.

## Chapter 1 - Ethical Mandate for Protecting Human Subjects

Human subject research associated with George E. Wahlen VAMC Salt Lake City HCS (VASLCHCS) must be carried out in an ethical manner (38 CFR 16.103(b)(1)). This Handbook is intended to provide important information to investigators, who involve human subjects in research approved by the VASLCHCS Research & Development Committee (R&D) and its sub-committees, and to other members of the research team. The documents discussed in this chapter represent important milestones in the evolving worldwide acceptance of ethical principles for the conduct of human subject research and in the development of protections for human research subjects in the United States.

- a. **The Nuremberg Code.** The modern history of human subject protections begins with the discovery after World War II of numerous atrocities committed by Nazi doctors in war-related human research experiments. The Nuremberg Military Tribunal developed ten principles as a means of judging their "research" practices, known as *The Nuremberg Code*. The significance of the Code is that it addressed the necessity of requiring the voluntary consent of the human subject and that any individual "who initiates, directs, or engages in the experiment" must bear personal responsibility for ensuring the quality of consent.
- b. **The Declaration of Helsinki.** Similar principles to The Nuremberg Code have been articulated and expanded in later codes, such as the World Medical Association *Declaration of Helsinki: Recommendations Guiding Medical Doctors in Biomedical Research Involving Human Subjects* (1964, revised 1975, 1983, 1989, 1996, 2000), which call for prior approval and ongoing monitoring of research by independent ethical review committees.
- c. **The Belmont Report.** Revelations in the early 1970s about the 40-year United States Public Health Service Study of Untreated Syphilis in the Negro Male at Tuskegee and other ethically questionable research resulted in 1974 legislation calling for regulations to protect human subjects and for a National Commission to examine ethical issues related to human subject research (i.e., the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research). The Commission's final report, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (79 FR 12065, April 17, 1979), defines the ethical principles and guidelines for the protection of human subjects.

Perhaps the most important contribution of *The Belmont Report* is its elucidation of three basic ethical principles:

- (1) **Respect for Persons** operationalized by obtaining informed consent, consideration of privacy, confidentiality, and additional protections for vulnerable populations;
- (2) **Beneficence** operationalized by weighing risks and benefits; and
- (3) **Justice** operationalized by the equitable selection of subjects.

*The Belmont Report* also provides important guidance regarding the boundaries and interface between biomedical research and the practice of medicine.

## Chapter 2 - Regulatory Mandate for Protecting Human Subjects

VASLCHCS policies, Department of Veterans Affairs (VA) and other Federal regulations require specific protections for human subjects. Investigators should be familiar with the following regulatory documents.

- a. **Department of Health and Human Services (DHHS) Regulations (45 CFR Part 46).** In May of 1974, the Department of Health, Education, and Welfare (later divided to form the DHHS and the Department of Education) codified its basic human subject protection regulations at 45 CFR 46, Subpart A. Revised in 1981 and 1991, the DHHS regulations presently include additional protections for pregnant women, human fetuses and neonates (Subpart B); prisoners (Subpart C); and children (Subpart D). The DHHS regulations are enforced by the Office for Human Research Protections (OHRP).

DHHS regulations at 45 CFR Part 46 Subpart A constitutes the Federal Policy (Common Rule) for the protection of human subjects. This Common Rule applies to any human subject research supported by any of the seventeen agencies of the Federal government that support human subject research (see Table 2.1).

<b>Table 2.1 Federal Common Rule Departments and Agencies</b>	
<b>Department / Agency</b>	<b>CFR Citation</b>
■ Department of Agriculture	■ 7 CFR Part 1c
■ Department of Energy	■ 10CFRPart 745
■ National Aeronautics and Space Administration	■ 14 CFR Part 1230
■ Department of Commerce	■ 15 CFR Part 27
■ Consume Product Safety Commission	■ 16 CFR Part 1028
■ International Development Cooperation Agency, Agency for International Development	■ 22 CFR Part 225
■ Department of Housing and Urban Development	■ 24 CFR Part 60
■ Department of Justice	■ 28 CFR Part 46
■ Department of Defense	■ 32 CFR Part 219
■ Department of Education	■ 34 CFR Part 97
■ Department of Veterans Affairs	■ 38 CFR Part 16
■ Environmental Protection Agency	■ 40 CFR Part 26
■ Department of Health and Human Services	■ 45 CFR Part 46
■ National Science Foundation	■ 45 CFR Part 690
■ Department of Transportation	■ 49 CFR Part 11
■ Central Intelligence Agency	■ Executive Order
■ Social Security Administration	■ Authorizing Statute

- b. **Department of Veterans Affairs (VA) Regulations (38 CFR Part 16).** In January of 1991, the VA joined 16 other Executive Branch Departments and Agencies in simultaneously adopting the Federal Policy (Common Rule) for the Protection of Human Subjects. Codified



by the VA at 38 CFR Part 16, the Common Rule is the same as that codified by DHHS as Subpart A of the DHHS regulations at 45 CFR Part 46, but does not include the additional DHHS Subparts. Additional VA regulations that are relevant to the protection of human subjects address patient rights (38 CFR 17.33), medical hospital care for research purposes (38 CFR 17.45), treatment of research related injuries to human subjects (38 CFR 17.85) and outpatient care for research purposes (38 CFR 17.92). These VA regulations are enforced by the Veterans Health Administration (VHA) Office of Research Oversight (ORO).

In general, VA human subject regulations apply to all human subject research conducted at the VA Medical Center (VAMC) or by VAMC employees or agents, or otherwise under the auspices of the VA including research using nonpublic patient data from VA records, using VA resources, published or presented with VA cited as supporting or conducting the research, or recruiting VA patients at VA facilities (VHA Handbook 1200.5(4.b)).

**Note:** Investigators receiving support from other Federal agencies, such as DOD or NIH, must meet requirements for the protection of human subjects of the funding source in addition to those of the VA (VHA Handbook 1200.5(4. c)).

- c. **Food and Drug Administration (FDA) Regulations (21. CFR Parts 50 and 56).** FDA has codified informed consent (21 CFR Part 50), IRB (21 CFR Part 56), and child protection (61 FR 20589 and 21 CFR Part 50, Subpart D) regulations that are almost identical to the DHHS regulations. Additional FDA regulations relevant to the protection of human subjects address Investigational New Drugs (21 CFR Parts 312 & 314), Radioactive Drugs (21 CFR Part 361), Biological Products (21 CFR Parts 600 & 601), and Investigational Devices (21 CFR Parts 812 & 814).

In general, FDA human subject regulations apply to clinical investigations and other research involving products regulated by FDA, including food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products, regardless of funding source.

IRB review and approval is required for all clinical investigations and all other research involving products regulated by FDA for human use, even where an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) is not required.

## Chapter 3 - VASLCHCS Policy for Protecting Human Subjects

As a matter of institutional policy, VASLCHCS meets the requirements of the DHHS and VA human subject protection regulations for all of its research, without regard to source of funding or other support. VASLCHCS also complies with the requirements of FDA regulations where applicable.

- d. **VASLCHCS Federalwide Assurance and IRB Registration.** The Common Rule requires that every institution engaged in Federally-supported human subject research file an "Assurance" of protection for human subjects (38 CFR 16.103(a)). The Assurance formalizes the institution's commitment to protect human subjects. The VHA Office for Research Oversight (ORO) coordinates IRB registration and Federalwide Assurance (FWA) filing for all VA facilities.

VASLCHCS maintains a Federalwide Assurance of Protection for Human Subjects (FWA001900) approved by the DHHS Office for Human Research Protections (OHRP). The VASLCHCS Medical Center Director is the institutional authority for establishing and empowering the UU IRB and serves as the Institutional Human Subject Signatory Official (Institutional Official or IO) for the VASLCHCS FWA.

The UU IRB is the "IRB of record" for VASLCHCS and is a subcommittee of the VASLCHCS Medical Research and Development (R&D) Committee (VHA Handbook 1200.5(5.a)).

VA policy does not permit use of commercial IRBs (VHA Handbook 1200.5(5.a)).

- e. **VASLCHCS FWA Covered Facilities.** VA policy at VHA Handbook 1200.5(3.h) clarifies that an "institution" includes a VA medical center or integrated VA health care system and its satellite facilities including community-based outpatient clinics. Accordingly, the VASLCHCS is comprised of the following facilities:

- George E. Wahlen VAMC, 500 Foothill Drive, Salt Lake City, UT 84148
- Nine Community Based Outpatient Clinics (CBOCs)

Research conducted at these facilities must be prospectively reviewed and approved by the UU IRB and R&D Committee.

## Chapter 4 - Human Subject Research vs. Non-Research Activities

All research involving human subject conducted at the VASLCHCS or by VASLCHCS employees or agents on VA official time must be reviewed by the UU IRB. Sometimes questions arise as to whether an activity is considered human subject research. This chapter is intended to provide a reference to assist investigators in determining when an activity is human subject research. When in doubt, investigators should contact the IRB Office.

All human subject research including research that qualifies as exempt from IRB review must be submitted to the Research Office for review by the IRB Chairperson or the IRB Vice-Chairperson. Please refer to Chapter 6 for guidance on determining whether activities deemed human subject research may be exempt from IRB review.

a. **Important Definitions for the Protection of Human Subjects in Research.** The following important definitions relating to human subject protections are provided here for convenience.

- (1) **Research.** VA regulations at 38 CFR 16.102(d) and the Common Rule define research as "**a systematic investigation, including research development, testing, and evaluation, designed to develop or contribute to generalizable knowledge.**" *Note: FDA regulations at 21 CFR 56.102(c) define research as "any experiment that involves a test article and one or more human subjects." FDA regulations note that "[the terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this par.]*
- (2) **Human Subject.** VA regulations at 38 CFR 16.102(f) and the Common Rule define human subject as "**a living individual about whom an investigator (whether professional or student) conducting research obtains (1) data through intervention or interaction with the individual or (2) identifiable private information.**" VA policy at VHA Handbook 1200.5(3.g) clarifies that human subjects may also include investigators, technicians, and other assisting investigators when they serve a "subject" role by being observed, manipulated, or sampled. *Note: FDA regulations at 21 CFR 56.102(e) define **human subject** as "an individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient."*
- (3) **Private Information.** Federal regulations define **private information** to include any information that an individual can reasonably expect will not be made public, and any information about behavior that an individual can reasonably expect will not be observed or recorded.
- (4) **Identifiable.** Federal regulations define **identifiable** to mean that the identity of the individual subject is or may readily be ascertained by the investigator or associated with the information.
- (5) **Minimal Risk.** Federal regulations at 45 CFR 46.102(f) and 21 CFR 56.102(i) define **minimal risk** to mean that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.
- (6) **Minimal Risk for Prisoners.** In the case of research involving prisoners, federal regulations at 45 CFR 46.303(d) define minimal risk as the probability and magnitude of physical or

psychological harm that is normally encountered in the daily lives, or in the routine medical, dental, or psychological examination of healthy persons.

(7) **Institutional Review Board (IRB).** An IRB is an appropriately constituted group that has been formally designated to review and monitor research involving human subjects. In accordance with the Common Rule, DHHS regulations, and FDA regulations, the IRB has responsibility for approving, requiring modification in (to secure approval), or disapproving research. The IRB also has the authority to suspend or terminate research for continued noncompliance with the Common Rule, DHHS regulations, and FDA regulations, or its own findings, determinations, and initial and continuing review procedures.

b. **Types of Human Subject Research.** The following examples illustrate common types of human subject research. These are examples only, and are not exhaustive of all human subject research.

(1) **Biomedical Research.** Biomedical research involves research (i) to increase scientific understanding about normal or abnormal physiology, disease states, or development; and (ii) to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device research, and cancer research are all types of Biomedical Research.

(2) **Social and Behavioral Research.** The goal of Social and Behavioral Research is similar to that of Biomedical Research--to establish a body of knowledge and to evaluate interventions--but the content and procedures often differ. Social and Behavioral Research involving human subjects focuses on individual and group behavior, mental processes, or social constructs and usually generates data by means of surveys, interviews, observations, studies of existing records, and experimental designs involving exposure to some type of stimulus or environmental intervention. (See also, Chapter 13, "Social and Behavioral Research.")

(3) **Clinical Research.** Clinical research involves the evaluation of biomedical or behavioral interventions related to disease processes or normal physiological functioning. Clinical research often, but not always, includes drugs, devices, or biological products regulated by the Food and Drug Administration (FDA). (See also, Chapter 12, "FDA-Regulated Research.")

(4) **Epidemiology Research.** Epidemiology research targets specific health outcomes, interventions, or disease states and attempts to reach conclusions about cost-effectiveness, efficacy, interventions, or delivery of services to affected populations. Some epidemiology research is conducted through surveillance, monitoring, and reporting programs--such as those employed by the Centers for Disease Control and Prevention (CDC)--whereas other epidemiology research may employ retrospective review of medical, public health, and/or other records. Because epidemiology research often involves aggregate examination of data, it may not always be necessary to obtain individually identifiable information. When this is the case, the research may qualify for exemption or expedited review. In all cases, **the IRB, not the individual investigator, will determine when IRB review of the activity is required.** (See also, Chapter 14).

(5) **Repository Research, Tissue Banking, and Databases.** Research utilizing stored data or materials (cells, tissues, fluids, and body parts) from individually identifiable living persons qualifies as human subject research, and requires IRB review. When data or materials are stored in a bank or repository for use in future research, the IRB must review a protocol

detailing the repository's policies and procedures for obtaining, storing, and sharing its resources, for verifying informed consent provisions, and for protecting subjects' privacy and maintaining the confidentiality of data. The IRB may then determine the parameters under which the repository may share its data or materials with, or without, IRB review of individual research protocols. New projects must utilize VA-sponsored tissue banks (VHA Directive 2000-043 "Banking of Human Research Subject's Specimens").

(6) **Pilot Studies.** Pilot studies involving human subjects are considered human subject research and require IRB review.

(7) **Human Genetic Research.** Genetic studies include but are not limited to: (a) pedigree studies (to discover the pattern of inheritance of a disease and to catalogue the range of symptoms involved); (b) positional cloning studies (to localize and identify specific genes); (c) DNA diagnostic studies (to develop techniques for determining the presence of specific DNA mutations); (d) gene transfer research (to develop treatments for genetic disease at the DNA level), (e) longitudinal studies to associate genetic conditions with health, health care, or social outcomes, and (f) gene frequency studies. Unlike the risks presented by many biomedical research protocols considered by IRBs, the primary risks involved in the first three types of genetic research are risks of social and psychological harm, rather than risks of physical injury. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. **Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review.** Because this is a developing field, there are some issues for which no clear guidance can be given at this point, either because not enough is known about the risks presented by the research, or because no consensus on the appropriate resolution of the problem yet exists. OHRP representatives have advised that "third parties," about whom identifiable and private information is collected in the course of research, are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB's can consider if informed consent from third parties can be waived in accordance with 38 CFR 16.116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate (see also, Chapter 9, item "h").

c. **Quality Assurance Activities vs. Human Subject Research.** Quality Assurance activities attempt to measure the effectiveness of programs or services (e.g., medical use evaluations) Quality Assurance activities constitute human subject research, and require IRB review, when they are designed or intended, at least in part, **to develop or contribute to generalizable knowledge.**

On the other hand, Quality Assurance activities that are designed solely for internal program evaluation purposes, with no external application or generalization, usually do not constitute human subject research, and usually do not require IRB review.

For example, suppose one of the VASLCHCS Sections conducts a review of patient records and then contacts patients to identify cases where recommended follow-up did not occur. If the sole intent is to improve the rate of follow-up at VASLCHCS, then the activity is not human subject research and does not require IRB review. However, if the intent of the activity, at least in part, includes extending the findings to patients at facilities outside VASLCHCS, or disseminating the findings in such a way that applicability outside VASLCHCS is stated or implied, then the activity does constitute human subject research, and does require IRB review.

In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal VASLCHCS purposes lead to a desire to generalize and disseminate the results for application outside VASLCHCS), the activity becomes research at the moment the intent to generalize the findings is formed, and the IRB should be contacted immediately. In such cases, the IRB will determine the conditions under which the investigator may pursue the relevant research objectives.

Where any disagreement arises about whether a Quality Assurance activity constitutes human subject research, the IRB, not the individual investigator, will determine when IRB review of such activities is required.

- d. **Research Activities vs. Innovative Treatments in Medical Practice.** In the course of medical practice, sound clinical judgment sometimes leads physicians to employ "innovative" treatments where more common treatments appear to be ineffective or otherwise unsuitable in addressing a patient's individual needs. Such innovative treatments employed on an occasional basis and solely for clinical purposes do not normally constitute human subject research and do not normally require IRB review.

However, the use of innovative treatments as part of a systematic investigation designed, at least in part, to develop or contribute to generalizable knowledge does constitute human subject research and does require prospective IRB review.

- e. **Research Activities vs. Medical Case Reports.** Generally speaking, a case report is not usually considered research because it is not usually "a systematic investigation designed to develop or contribute to generalizable knowledge" therefore it does not come under the rubric of the IRB or R&D Committee. Further, the case report presentation, whether by lecture or publishing, is executed by the physician of record, meaning that the patient's own physician is reporting the case and already has identified the patient and has access to the clinical data. If the presentation uses photographs, initials, or any other information that may possibly identify the patient, then written permission or a separate consent form for this purpose is required.

There does not appear to be a limit on the number of cases from one's own patients that form a case report and if exceeded, moves the situation into the category of retrospective chart review and then requires IRB approval. Usually, a (non-research) case report summarizes one case (or occasionally two, or at most three, cases) to emphasize a discrete instance of disease. However, it is the nature of the report, not the absolute number of cases that determines whether or not the activity involves human subject research. A non-research case report may not involve a systematic investigation characterized as developing or contributing to generalizable knowledge. A non-research case report is limited to an account of an observation or a description of a disease process that has little scientific merit and is not subjected to scientific analysis. It is not presented as a systematic investigation designed to contribute to generalizable knowledge. A (non-research) case report should be presented in such a way that it is readily distinguishable from a research report, which usually contains data with statistical analysis, or at a least a systematic qualitative analysis that substantiates the science and the conclusion and thus constitutes a contribution to generalizable knowledge.

- f. **Research Activities vs. Commercial Services.** VASLCHCS facilities and laboratories may occasionally provide tests or other services to non-VASLCHCS researchers solely on a commercial

basis (e.g., VASLCHCS performs MRIs for non-VASLCHCS investigators solely on a commercial basis).

Provision of such services solely on a commercial basis does not constitute VASLCHCS human subject research and does not require UU IRB review, provided that all of the following conditions are met:

- (1) The research is not otherwise conducted at VASLCHCS;
- (2) The research does not otherwise involve VASLCHCS employees or agents (e.g., as co-investigators, in planning or analysis, or receiving publication credit);
- (3) The commercial services are genuinely non-collaborative, meriting neither professional recognition nor publication privileges;
- (4) The commercial services adhere to commonly recognized professional standards for maintaining privacy and confidentiality; and
- (5) The commercial services are conducted under a valid contract.

However, if VASLCHCS personnel are involved in any way that is more than merely providing a commercial service, then prospective review and approval of the UU IRB is required.

## Chapter 5 - Investigator Responsibilities for Protecting Human Subjects

The ethical conduct of research is a shared responsibility. It requires cooperation, collaboration, and trust among the institution, investigators and their research staff, the subjects who enroll in research, and the IRB. A clear delineation of the responsibilities of each of these parties can help in assuring protections for the participants who volunteer for research as well as compliance with Federal regulations. This Investigator Handbook is limited to the responsibilities of those who conduct human subject research or who are involved in the informed consent process.

Please also see Chapter 16 for information regarding educational and credentialing requirements for researchers.

- a. **Principal Investigators.** It is VASLCHCS policy that **Principal Investigators must have VA appointments.** As the individual responsible for the implementation of research, the principal investigator bears direct responsibility for protecting every research subject (VHA Directive 1200.5(3.n.)). This responsibility starts with protocol design, which must minimize risks to subjects while maximizing research benefits. The principal investigator must also include a data and safety monitoring plan. In addition, the principal investigator and all members of the research team must comply with the findings, determinations, and requirements of the IRB. The principal investigator must also be responsible for the adequacy of both the informed consent document and the informed consent process, regardless of which members of the research team actually obtain and document consent. (VHA Handbook 1200.5(10)). A Responsible Investigator is also required if the Principal Investigator is not qualified to be responsible for all study-related healthcare decisions.

Principal Investigators must:

- (1) Review the VASLCHCS's FWA, this Handbook and the IRB Standard Operating Procedures manual (currently being revised), VA Regulations for Protection of Human Research Subjects, relevant DHHS and FDA regulations, and the Belmont Report.
- (2) Ensure that the research is conducted at all times in compliance with all applicable Federal, State, and local regulatory requirements and with the determinations of the UU IRB.
- (3) Ensure that the protocol is properly documented that there are adequate resources and facilities to carry out the research.
- (4) Ensure that all human subject research, which they conduct at VASLCHCS or on official VA time, has received prospective review and approval by the UU IRB.
- (5) Ensure that continuing IRB review and approval of the research are secured in a timely fashion.
- (6) Ensure that no changes in approved research are initiated without prior approval of the UU IRB and VASLCHCS R&D, except where necessary to eliminate apparent immediate hazards to subjects; and no research may be continued beyond the IRB-designated approval period.
- (7) Ensure that the UU IRB and VASLCHCS R&D is notified promptly of (i) any injuries or unanticipated problems involving risks to subjects or others; (ii) any serious adverse events experienced by subjects; (iii) any adverse events reported to the study sponsor; and (iv) any



serious or continuing noncompliance with applicable regulatory requirements or determinations of the IRB of which they become aware and (v) any protocol deviations (see UU IRB Guidance Document for Protocol Deviations). (See, Chapter 11).

- (8) Report all events to the DSMB/DMC, if used, and report a summary of the DSMB/DMC findings to the UU IRB and VASLCHCS R&D.
- (9) Maintain complete and accurate records regarding all communications with the UU IRB and the VASLCHCS R&D, the sponsor, and any Federal Agency, and make such records available to the VASLCHCS Institutional Official and/or the VASLCHCS Research Compliance Officer immediately upon request.
- (10) Make a final report to the UU IRB, VASLCHCS R&D and to the sponsor within three months after the completion or discontinuance of a research project, or of withdrawal of the exemption for a research project.

If the investigator leaves the VASLCHCS facility, the original research records must be retained at the VASLCHCS (VHA Handbook 1200.5(10.i)). Prior to leaving, the investigator must confirm in writing where all records will be stored and when the record destruction is scheduled to occur.

- b. **Responsible Investigators. All Responsible Investigators must have a paid VA appointment.** A Responsible Investigator (RI) is required if the Principal Investigator (i) has a Without Compensation (WOC) VA appointment; (ii) is a student, resident or fellow; or (iii) is not credentialed to perform/supervise the study procedures. An RI is also required if the PI is not qualified to be responsible for all study-related healthcare decisions.
- c. **Co-Investigators.** Co-investigators include individuals who make a significant contribution to the creation and/or conduct of the study. (VHA Handbook 1200(5.k)). Co-investigators work under the direct supervision of the Principal and/or Responsible Investigator. **Co-investigators who work at the VASLCHCS and/or have contact with VA subjects and/or have access to VA information systems must have a VA appointment.** Co-Investigators who are based at an affiliate or other outside institution, and who do not come to the VA or directly interact with VA research participants do not need a VA appointment.
- d. **Other Members of the Research Team.** Every member of the research team is responsible for protecting human subjects. Study coordinators, nurses, research assistants, and all other research staff have a strict obligation to comply with all IRB determinations and procedures; adhere rigorously to all protocol requirements; inform investigators of all adverse reactions or unanticipated problems, or protocol deviations involving risks to subjects or others; oversee the adequacy of the informed consent process; and take whatever measures are necessary to protect the safety and welfare of subjects.

Researchers at every level are responsible for notifying the UU IRB and the VASLCHCS R&D promptly of any serious or continuing noncompliance with applicable regulatory requirements or determinations of the UU IRB of which they become aware, whether or not they themselves are involved in the research. Researchers may also notify the Research Compliance Officer directly of any compliance concerns they may have.

## Chapter 6 - IRB Roles and Authorities

Because investigators have an obligation to conduct their research in accordance with the determinations of the UU IRB, it is necessary to discuss the role and authority of the IRB in reviewing, approving, and conducting continuing oversight of research per our FWA with the University of Utah, the VASLCHCS investigators can submit requests only to the four medical IRB panels.

- a. **Purpose and Mission of the IRB.** The IRB's primary responsibility is to protect the rights and welfare of participants involved in human subject research (38 CFR 16.109). In doing so, the IRB monitors human subject research to determine that it is conducted ethically, and in compliance with applicable VA and Federal regulations, applicable State and local law, VASLCHCS's Federalwide Assurance, Memorandum of Understanding, and VASLCHCS's policies and procedures for protecting human subjects.

The IRB fulfills these responsibilities by conducting prospective and continuing review of human subject research, including review of the protocol and grant applications or proposals (regardless of the funding source), the informed consent process, procedures used to enroll subjects, and any adverse events or unanticipated problems reported to the IRB. Prospective review and approval of research or changes to previously approved research ensures that research is not initiated without IRB review and approval.

- b. **Scope of the IRB's Authority.** The UU IRB has regulatory authority to take any action necessary to protect the rights and welfare of human subjects in the VASLCHCS research program. Pursuant to VA regulations at 38 CFR 16.109(a), the UU IRB has authority and responsibility for approving, requiring modification in (to secure approval), or disapproving human subject research. The IRB also has the authority to suspend or terminate research for continued noncompliance with the Common Rule, VA, DHHS and FDA regulations, or its own findings, determinations, and requirements (38 CFR 16.113). The UU IRB has the authority to observe and/or monitor VASLCHCS research to whatever extent it considers necessary to protect human subjects. No VASLCHCS official or VASLCHCS committee may permit the conduct of human subject research that has not been approved by a VASLCHCS-designated IRB.

Research that has been approved by the IRB remains subject to any additional review deemed appropriate by the R&D Committee. VASLCHCS retains the authority to prohibit conduct of research within its facilities or by its employees or agents that VASLCHCS deems not to be in its best interests (e.g., research that is not consistent with the mission of VASLCHCS; research that would require skills or resources that are not readily available; or research that might result in unacceptable fiscal or reputational risks).

- (1) **Requirement for Prospective Review and Approval.** All human subject research conducted at any VASLCHCS facility or by any VASLCHCS employee or agent must be prospectively reviewed and approved by the UU IRB. **No human subject research may be initiated or continued at any VASLCHCS component or by any VASLCHCS employee or agent without prospective approval of the UU IRB.**
- (2) **Adding a New Site to an Existing Approved Protocol.** Any VASLCHCS component or investigator desiring to add a new site to an existing IRB-approved protocol must submit the request with all required materials to the UU IRB.

- (3) **Power to Take Action.** The UU IRB is empowered to take any action necessary to protect the rights and welfare of human subjects participating in VASLCHCS research. The IRB has the authority to approve, require modifications in, or disapprove the respective investigator's human subject research.
- (4) **Power to Suspend or Terminate Enrollment.** The IRB may suspend or terminate the enrollment and/or ongoing involvement of human subjects in research as it determines necessary for the protection of those subjects, especially in instances of serious or continuing noncompliance. The IRB has the authority to observe and/or monitor the respective institution's human subject research to whatever extent it considers necessary to protect human subjects and assure compliance with applicable laws and regulations.
- (5) **Cases of Serious or Continuing Noncompliance.** In cases of serious or continuing noncompliance, the IRB may: (i) disqualify an investigator from conducting a particular research project or research altogether at the institution; (ii) require education and training in the ethics and regulations of human subject research; or (iii) any other reasonable measure deemed appropriate to protect the rights and welfare of research subjects.
- (6) **Access to Regulatory Correspondence.** All persons conducting research within any VASLCHCS component, and all persons acting as employees or agents of VASLCHCS regardless of location, must promptly provide the UU IRB with copies of any reports, audit findings, or correspondence to or from any regulatory agency (such as OHRP or FDA) that bear upon the protection of human subjects in research in which they are involved.

- c. **Requests for Exemption from IRB Review.** All human subject research that is conducted at VASLCHCS or by employees or agents of VASLCHCS must receive prospective review and approval by the UU IRB or be verified as exempt by the UU IRB Chairperson or an IRB Vice-Chairperson. Investigators may request exemptions from IRB review by submitting a written request to the IRB chair, which lists the categories under which an exemption can be granted.

Exemptions include the following:

- (1) **Exempt Research in Educational Settings.** Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from Federal regulations in accordance with 38 CFR 16.101(b)(1). This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed. Even if the research is exempt, the investigator has an ethical obligation to respect and safeguard students' rights and welfare.
- (2) **Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior.** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is ordinarily exempt under Federal regulations at 38 CFR 16.101(b)(2).

When the subjects are **adults**, this exemption applies UNLESS: (a) information is recorded in an identifiable manner (either directly or indirectly using codes or other identifying links); AND (b) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. *Note: The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the*

*information collected is both identifiable and sensitive, except in the case of children as follows.*

This exemption applies to research involving **children**, EXCEPT that: (a) research involving survey or interview procedures with children is NOT EXEMPT; and (b) research involving observation of the public behavior of children is NOT EXEMPT if the investigator participates in the actions being observed.

- (3) **Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior.** If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt under 38 CFR 16.101(b)(3) where: (a) the subjects are elected or appointed public officials or candidates for public office; or (b) Federal statutes require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter. *Note: Condition (b) regarding Federal statutes rarely applies. The VASLCHCS R&D designee will consult with OHRP if it receives an exemption request based on absolute confidentiality under a Federal statute.*

If not exempt under the conditions described above, the IRB may sometimes utilize expedited procedures for review and approval of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior.

- (4) **Exempt Use of Existing Materials.** Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated may be exempt from IRB review and informed consent requirements.

Such research may be exempt under VA regulations at 38 CFR 16.101(b)(4) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers (e.g., codes) linked to the subjects. If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects.

Retrospective studies using existing materials occasionally entail greater than minimal risks to subjects and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited reviewer had concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

- (5) **Exempt Research and Demonstration Projects with Approval of Department or Agency Heads.** 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; or (d) possible changes in methods or levels of payment for benefits or services under those programs.

(6) **Exempt Taste and Food Quality Evaluation and Consumer Acceptance Studies.** Taste and food quality evaluation and consumer acceptance studies are exempt from IRB review if: (a) wholesome foods without additives are consumed or (b) a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration (FDA) or approved by the Environmental Protection Agency (EPA) or the Food Safety and Inspection Service of the U.S. Department of Agriculture. This also applies to FDA regulated research.

- d. **Review by the Convened IRB.** VA regulations at 38 CFR 16.108(b), the Federal Policy (Common Rule) for the Protection of Human Subjects, and FDA regulations require that the UU IRB conduct initial and continuing reviews of all non-exempt research at convened meetings at which a majority of the members are present, unless the research falls into one or more of the categories appropriate for expedited review.

Please refer to Chapter 18 for details on submitting research to the IRB for review and approval.

- e. **Continuing Review by the Convened IRB.** The UU IRB is required to conduct "substantive and meaningful continuing review" of research at intervals appropriate to the degree of risk, but not less than once per year (38 CFR 16.103 & 16.109(b)(4)). Continuing reviews will be conducted by the convened IRB unless the research falls into one or more of the categories appropriate for expedited review (as discussed later in this chapter). Investigators may submit their progress report directly to the IRB for continuing review on the electronic system, which requests information necessary for the IRB to conduct a substantive and meaningful continuing review. The Study Closure Report - is required for all studies where research related activities at the VASLCHCS have been completed including analysis of identifiable/coded data, studies that were never conducted, and studies that have been terminated.
- f. **Expedited Review of Research.** VA regulations, the Federal Policy (Common Rule), and FDA regulations permit the IRB to review research through an expedited procedure if:

- (1) The research constitutes a minor change in previously approved research during the period for which approval is authorized, **or**
- (2) The research is not greater than minimal risk and falls within the categories on the November 9, 1998 DHHS-FDA list of research eligible for expedited IRB review (see item "h" below).

Under an expedited review procedure, the IRB Chairperson or an experienced reviewer designated by the Chairperson, may review and approve the research on behalf of the IRB, request additional information, or forward the application to the fully convened IRB. Investigators may request expedited review if completely justified. Necessary documentation for submission to the IRB can be found at [www.utah.edu/irb](http://www.utah.edu/irb).

- g. **Expedited Review of Minor Changes in Previously Approved Research.** The UU IRB may utilize expedited procedures to review a proposed change to previously approved research if it represents a minor change to be implemented during the previously authorized approval period. VASLCHCS defines a minor change to be one that makes **no substantial alteration** in ANY of the following:

- (1) The probability or magnitude of risks to subjects.

- (2) The research design or methodology.
- (3) The number of subjects enrolled in the research.
- (4) The qualifications of the research team.
- (5) The facilities available to support safe conduct of the research.
- (6) The likelihood of subjects' willingness to participate.
- (7) Any factor that might warrant convened review.

h. **Expedited Review of Research in Specified Categories.** Investigators may request the IRB utilize expedited procedures for the initial or continuing review of research that is no greater than minimal risk and falls within the FDA/DHHS specified expedited review categories (63 FR 60353-60356 and 60364-60367, November 9, 1998). These categories **do NOT apply to research involving prisoners.**

- (1) **Expedited Category #1.** Clinical studies of drugs and medical devices only when condition (a) or (b) is met:
  - (a) Research on **drugs** for which an investigational new drug application (21 CFR 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.)
  - (b) Research on medical **devices** for which (i) an investigational device exemption application (21 CFR Part 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/approved labeling.
- (2) **Expedited Category #2.** Collection of blood samples by finger stick, heel stick, ear stick, or venipuncture as follows:
  - (a) **From healthy, nonpregnant adults** who weigh at least 110 pounds. For these subjects, the amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week; or
  - (b) **From other adults and children,** considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, and the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
- (3) **Expedited Category #3.** Prospective collection of biological specimens for research purposes by noninvasive means. Examples:
  - (a) Hair and nail clippings in a non-disfiguring manner.

- (b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction.
  - (c) Permanent teeth if routine patient care indicates a need for extraction.
  - (d) Excreta and external secretions (including sweat).
  - (e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue.
  - (f) Placenta removed at delivery.
  - (g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor.
  - (h) Supra- and sub gingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and the process is accomplished in accordance with accepted prophylactic techniques.
  - (i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings.
  - (j) Sputum collected after saline mist nebulization.
- (4) **Expedited Category #4.** Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/approved for marketing. (Studies intended to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.) Examples:
- (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of energy into the subject or an invasion of the subject's privacy.
  - (b) Weighing or testing sensory acuity.
  - (c) Magnetic resonance imaging.
  - (d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.
  - (e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
- (5) **Expedited Category #5.** Research involving materials (data, documents, records, or specimens) that have been collected, or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis). *Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects. 45 CFR 46.101(b)(4). This listing refers only to research that is not exempt.*

The intent of the drafters was to define two categories here, each appropriate for expedited review.

- (a) Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.
- (b) Non-exempt research involving materials that will be collected in the future (i.e., prospectively) for a non-research purpose (see below).

Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents, records or specimens) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under DHHS regulations at 45 CFR 46.101(b)(4) because the materials in these studies are not in existence at the time the study is proposed and initiated.

However, the IRB may utilize **expedited procedures** to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

- (6) **Expedited Category #6.** Collection of data from voice, video, digital, or image recordings made for research purposes.
- (7) **Expedited Category #7.** Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies. *Note: Some research in this category may be exempt from the HHS regulations for the protection of human subjects (45 CFR 46.101(b) (2) and (b)(3)). This listing refers only to research that is not exempt*
- (8) **Expedited Category #8.** Continuing review of research previously approved by the convened IRB as follows:
  - (a) Where (i) the research is permanently closed to the enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long-term follow-up of subjects; **or**
  - (b) Where no subjects have been enrolled and no additional risks have been identified; **or**
  - (c) Where the remaining research activities are limited to data analysis.
- (9) **Expedited Category #9.** Continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that



the research involves no greater than minimal risk and no additional risks have been identified.

- i. **Protocol Revisions, Modifications, and Amendments.** Revisions, modifications, or amendments to a research protocol must be summarized on the IRB Form, and must be incorporated into the protocol summary. This practice ensures that there is only one complete protocol with the revision dates noted on first page of the protocol itself. This procedure is consistent with the procedure used for revised and approved informed consent documents, which then supercede the previous one.
- j. **Review of Reports of Unanticipated Problems, Protocol Deviations, or Adverse Events.** Investigators are required to notify the IRB promptly of any unanticipated problems involving risks to subjects or others that occur in research conducted under the purview of the UU IRB. Investigators are also required to report promptly to the IRB any adverse event that is reported to the FDA or the sponsor in accordance with FDA requirements.

The UU IRB should receive the completed IRB Form, Reporting Adverse Events and Unanticipated Problems, from the investigator **within 10 working days** of knowledge of the event. Deaths must be reported immediately (Immediately usually means within one day of the knowledge of the death.) (See also, Chapter 11).

- (1) **Notice of IRB Determination(s) to Investigator.** The investigator is notified in writing of the IRB's determinations, even if no further action is necessary on the part of the investigator.
  - (2) **Notice of IRB Determination(s) to Agencies.** It is the responsibility of the IRB Chairperson to provide prompt written notification to relevant Federal Agencies, including OHRP and FDA (for FDA-regulated research), and the VASLCHCS R&D Committee of any unanticipated problems involving risks to subjects or others, if the resolution includes suspension or termination of the protocol.
- k. **Review of Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) Reports.** Investigators are required to forward DSMB or DMC reports to the IRB. The review of DSMB or DMC reports is handled in the same manner as protocol revisions, modifications, and amendments.
  - l. **IRB Relationships within VASLCHCS.** The UU IRB relies upon the VASLCHCS R&D to seek review from all applicable sub-committees, such as:
    - (1) The Subcommittee on Research Safety which reviews the use of biological hazards, human cell or tissue samples, select chemicals, controlled substances, biologics, recombinant DNA, radiation exposure, etc.
    - (2) The Institutional Animal Care and Use Committee which reviews all scientific protocols using live animals.

All persons conducting research within VASLCHCS, and all persons acting as employees or agents of VASLCHCS regardless of location, must comply with all requirements of the UU IRB in the conduct of human research. Such persons must provide the UU IRB with copies of any reports or correspondence to or from any regulatory or compliance enforcement Federal agency, such as ORO, OHRP, or FDA, that exercises oversight over the protection of human subjects in research in which they are involved.

- m. **Appeal of IRB Determinations.** No VASLCHCS committee or VASLCHCS official may set aside or overrule a determination by the UU IRB to disapprove or require modifications in VASLCHCS's human subject research. No VASLCHCS committee or VASLCHCS official may permit the conduct of human subject research that has not been approved by an IRB officially designated by VASLCHCS. The UU IRB must provide the research investigator with a written statement of its reasons for disapproving or requiring modifications in proposed research and must give the investigator an opportunity to respond in person or in writing. The UU IRB will evaluate the investigator's response in reaching its final determination.
- n. **Disagreements Among Designated IRBs in Multi-Center Research.** Cooperative Studies Program (CSP) Guidelines (January 2001) state that although it is the preference of the CSP that a single standard consent form is used at all participating Medical Centers, the ultimate responsibility for the welfare of the patient resides at the individual Medical Center. If the IRB from a participating Medical Center makes suggestions for changes, they will be seriously considered. Similarly, local variations can be incorporated into a standard document for use in all or most Medical Centers. When necessary and appropriate, variations across centers will be permitted with the approval of the Director, Cooperative Studies Program Coordinating Center (CSPCC). Major changes must have the approval of the CSPCC Human Rights Committee.
- o. **Relationship of the UU IRB to IND/IDE Sponsors.** Unless specifically required by an Investigational New Drug Application (IND) or Investigational Device Exemption (IDE) sponsor or by the IRB, no written notifications of IRB decisions will be provided to IND/IDE Sponsors by the IRB. The Principal Investigator serves as the communications link between the IRB and the Sponsor for this purpose. For FDA regulated test articles, such linkage is agreed to by the sponsor and principal investigators when they sign the FDA Form 1572, Statement of Investigator.
- p. **Responsibilities to Regulatory Agencies.** The UU IRB must comply with the requirements of all relevant regulatory and compliance enforcement agencies or offices, including ORO, OHRP, and FDA. Copies of any reports or correspondence (e.g., notices of non-compliance, on-site serious adverse events, research misconduct, etc.) to or from such agencies concerning VASLCHCS research must be provided by the UU IRB to the R&D Committee, which shall determine whether any additional notifications are necessary. See Chapter 11 for a discussion of investigators' reporting responsibilities to the IRB.
  - (1) **Allegations of Non-compliance.** VA regulations at 38 CFR 16.103 (b)(5) require that the VAMC "promptly" report allegations of serious or continuing noncompliance with the governing regulations. VASLCHCS policy requires that such allegations be reported within 5 working days.

The OHRP Federal-Wide Assurance (FWA) and DHHS regulations at 45 CFR 46.103(b)(5)(i) obligate VASLCHCS to report allegations of serious or continuing non-compliance promptly to OHRP (see OHRP website for designated regional contacts). Copies of these reports should be simultaneously submitted to ORO. If there is an Investigational New Drug (IND) or an Investigational Device (IDE) involved in the research, the FDA needs to be notified per 21 CFR 56.108(b)(2).

The VASLCHCS should also consider whether the funding agency, for example, National

Institutes of Health (NIH) might also expect to be informed of serious non-compliance on a grant or contract. For example, the existence of substantial evidence to support the allegation may mandate reporting an ongoing review of a project, to the relevant department/agency official, irrespective of whether there is formal suspension of the research by the IRB.

Within VASLCHCS, allegations of serious or continuing non-compliance must be reported to the IRB Chairperson, ACOS/R&D, R&D Committee, Research Compliance Officer, Institutional Officer and Compliance Officer at the VISN level, if there is one.

- (2) **Serious Adverse Events (SAEs).** ORO's November 12, 2003 memorandum "What to Report to ORO: ACTION" requires that when an adverse event (or imminent threat of an adverse event) results in a **substantive IRB action**, then the IRB's determination to take such action must be reported to the ORO Regional Officer within **10 working days**. **Substantive IRB actions** materially alter the substance and meaning of a protocol, informed consent process or document, investigator status, including but not limited to restriction, suspension or termination of a study or investigator participation, and actions taken to prevent future occurrence(s) of the adverse event.

Regardless of IRB action, all **unexpected deaths** of research subjects must be reported to the ORO Regional Officer no later than **2 working days** after the IRB is informed of the death. (ORO Memorandum, "What to Report to ORO: ACTION," November 12, 2003). The VASLCHCS Research Compliance Officer is responsible for coordinating notification to ORO.

- (3) **Suspension or Termination of IRB Approval.** VA policy requires that for cause suspensions and terminations be reported to ORO within 10 working days (38 CFR 16.113; see also, ORO Memorandum, "What to Report to ORO: ACTION," November 12, 2003).

The OHRP Federal-Wide Assurance (FWA) and DHHS regulations at 45 CFR 46.103(b)(5)(ii) obligate VASLCHCS to report suspensions or terminations of IRB approval promptly to OHRP (see OHRP website for designated regional contacts). Copies of these reports should be simultaneously submitted to ORO. If there is an Investigational New Drug (IND) or an Investigational Device (IDE) involved in the research, the FDA needs to be notified per 21 CFR 56.108(b)(3).

In most cases, the funding agency, for example, National Institutes of Health (NIH) also expects to be informed of suspension or termination of IRB approval of research supported under a grant or contract.

- (4) **Unanticipated problems involving risks to subjects or others.** The OHRP Federal-Wide Assurance (FWA) and DHHS regulations at 45 CFR 46.103(b)(5)(i) obligate VASLCHCS to report unanticipated problems involving risks to subjects or others promptly to OHRP (see OHRP website for designated regional contacts).

Under DHHS regulations, "unanticipated problem" means any research-related event involving risk to anyone associated with the research in any way (including investigators and research assistants) that is not included in the protocol and informed consent document. See Chapter 11 for a more detailed discussion of unanticipated problems.

Copies of reports of unanticipated problems should be simultaneously submitted to ORO. If there

is an Investigational New Drug (IND) or an Investigational Device (IDE) involved in the research, the FDA needs to be notified per 21 CFR 56.108(b)(1).

- (5) **Research Misconduct.** VA policies for reporting research misconduct are currently under development and will be provided in VHA Handbook 1200.14. VA policy requires that all initiations of inquiries and investigations of research misconduct, including fabrication, falsification, or plagiarism in proposing, performing or reviewing research, or in reporting results, be reported to ORO. (ORO Memorandum, "What to Report to ORO: ACTION," November 12, 2003 and the forthcoming VASLCHCS Medical Center Policy 151-017 Scientific Misconduct in Research in).
  
- q. **Privacy Board Functions and Determinations.** The UU IRB serves as the VASLCHCS Privacy Board for research related issues as required by HIPAA, 45 CFR 164.501, 164.508, 164.512(i). Functions include review and determinations of requests for Waiver or Alteration of Authorization to use or disclose Protected Health Information in Research. The VA Privacy Officer reviews each new study for privacy issues and reports to the Research Review Committee.

## Chapter 7 - IRB Review: Regulatory Criteria for Approval of Research

The investigator initiates the IRB process by submitting an application requesting permission to conduct research involving human subjects. The IRB must follow specific regulatory criteria for the approval of research. These criteria are presented here to help investigators in preparing materials to submit to the IRB.

VA regulations at 38 CFR 16.111, DHHS regulations at 45 CFR 46.111, FDA regulations at 21 CFR 56.111, and the Federal Policy (Common Rule at Section 111) delineate specific criteria for the approval of research. The UU IRB will determine that all of the required criteria are satisfied before approving proposed research.

- a. **Risks are Minimized.** The IRB must consider the overall level of risk to subjects in evaluating proposed research. In general, the regulations require that the IRB distinguish research that is "greater than minimal risk" from research that is "no greater than minimal risk." Under specific circumstances, research that is no greater than minimal risk may be eligible for expedited review, waiver or alteration of informed consent requirements, or waiver of the requirement to obtain written documentation of consent.

Under VA regulations at 38 CFR 16.102(i) and the Common Rule, "minimal risk means that the probability and magnitude of harm or discomfort in the research are not greater in and of themselves than those encountered in daily life or during the performance of routine physical or psychological examinations or tests."

In order to approve research, the IRB must determine that risks are minimized by using procedures that are consistent with sound research design and do not expose subjects to unnecessary risks (38 CFR 16.111(a)(1)). Whenever appropriate, the research should utilize procedures already being performed on the subjects for diagnostic or treatment purposes.

The IRB is expected to consider the research plan, including the research design and methodology, to determine that there are no flaws that would place subjects at unnecessary risk. When the research design presents unnecessary or unacceptable risks to subjects without commensurate benefits to the subjects or to others, the research cannot ethically proceed and cannot be approved by the IRB.

In order to ascertain whether the research project is adequately designed and thus subjects protected, the IRB reserves the authority to seek opinions from consultants on proposed research and its design. The IRB may determine that the proposed research must be re-designed to enhance subject autonomy, maximize benefits, reduce risks, select subjects equitably, minimize undue influence or coercion, or otherwise protect the rights and welfare of human subjects.

The IRB will also consider the qualifications of the research team. Clinicians are expected to maintain appropriate professional credentials and licensing privileges. Overall, the research team must possess the professional and educational qualifications, as well as the resources, to conduct the research project and to protect the rights and welfare of subjects.

When evaluating research, the VASLCHCS carefully examines not only the risk of **physical harm** but also the risk of **psychological and social harms**. For example, the IRB considers:

- (1) The potential for participants to experience stress, anxiety, guilt, or trauma that can result in

genuine psychological harm.

- (2) The risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, reputation; stigmatization; and damage to social relationships.
- (3) Whether information is being collected on other living individuals in addition to the primary "target" subjects. The IRB will consider the risk of harm to those "non-target" individuals, as well. Collecting any identifiable, private information about any living individual constitutes human subject research. The IRB may require additional protections, study redesign, or the informed consent of "non-target" individuals (unless the requirement for informed consent can be waived).

In order to mitigate such risks, the UU IRB reviews proposed research for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in the research.

- b. **Risks Are Reasonable Relative to Anticipated Benefits.** In order to approve research, the IRB must determine that the risks of the research are reasonable in relation to the anticipated benefits (if any) to subjects and/or to the importance of the knowledge that may reasonably be expected to result (38 CFR 16.111(a)(2)).

The IRB develops its risk/benefit analysis by evaluating the most current information about the risks and benefits of the interventions involved in the research, in addition to information about the reliability of this information. The IRB will consider only those risks that result from the research, and will not consider long range effects (e.g., public policy implications) of applying the knowledge gained in the research.

- c. **Selection of Subjects is Equitable.** In order to approve research, the IRB must determine that the selection of subjects is equitable (38 CFR 16.111(a)(3)). To this end, VASLCHCS investigators must provide details of the proposed involvement of humans in research, including the characteristics of the subject population, anticipated numbers, age ranges, and health status. The proposed research should specify the gender and racial/ethnic composition of the subject population, as well as criteria for inclusion or exclusion of any subpopulation.

If ethnic, racial, and gender estimates are not provided as background information for initial review, and enrollment statistics are not provided for continuing review, **the investigators must provide a clear rationale for exclusion of this information.** For additional information, IRB members and investigators should refer to Section 492B of the Public Health Service Act, and the NIH Guide for Grants and Contracts, Vol. 23, Number 11, March 18, 1994.

In making the determination that subject selection is equitable, the IRB will evaluate the purposes of the research and the research setting, and will be especially cognizant of issues involving potentially vulnerable subject populations, which may include children, pregnant women, prisoners, handicapped or mentally disabled persons, or economically or educationally disadvantaged persons.

The IRB will carefully examine inclusion-exclusion criteria and recruitment procedures in order to determine that the burdens and benefits of the research are being distributed equitably.

- (1) **Inclusion of Non-Veterans.** Non-veterans may be entered into VASLCHCS 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 (see VHA Handbook 1200.5(16.a)).

- (2) **Inclusion of Females and Minorities.** It is the policy of VASLCHCS that females and members of minority groups and their sub-populations (as described in the VHA Handbook 1200.9) should be included in all biomedical and behavioral research projects involving human subjects, **unless** compelling scientific justification is provided that inclusion is inappropriate with respect to health of the subjects or the purpose of the research.

The IRB will remain mindful of the desirability of including both males and females as research subjects and will not permit the **arbitrary** exclusion of persons of reproductive age. Exclusion of such persons must be fully justified and based on sound scientific rationale.

- (3) **Inclusion of Non-English Speaking Participants.** Non-English speaking participants should not be systematically excluded because of inconvenience in translating informed consent documents (see also, item "e" below).
- (4) **Inclusion of Children.** Absent a waiver granted by the Chief Research and Development Officer, research involving children shall not be conducted by VA investigators while on official duty or at VA facilities or approved off-site facilities (VA Directive 2001-028, April 27, 2001).

- d. **Informed Consent Will Be Obtained.** In order to approve research involving adults as subjects, the IRB must determine that legally effective informed consent will be sought and obtained from each prospective subject or the subject's legally authorized representative (38 CFR 16.111(a)(4)), unless informed consent requirements can be waived or altered under Federal regulations. Any such waiver or alteration must be consistent with applicable Federal and State laws and regulations.

Where consistent with state law, VA policy recognizes as legally authorized representatives (1) persons appointed as health care agents under a Durable Powers of Attorney for Health Care; (2) court appointed guardians; (3) next of kin in the following order: spouse, adult child, parent, and adult sibling. However, VA policy limits the conditions under which the IRB may approve the use of consent from legally authorized representatives.

**(1) Considerations for Reviewing Informed Consent Process:**

- (a) Informed consent may only be sought under circumstances that minimize the possibility of coercion or undue influence and that provide the subject or legally authorized representative with sufficient opportunity to consider whether or not the subject will participate.
- (b) Information for informed consent must be presented in language that is understandable to the subject or legally authorized representative (see also, item "e" below for additional considerations for non-English speakers).
- (c) No informed consent process may include any exculpatory language (i) through which the subject is made to waive, or appear to waive, any of his/her legal rights; or (ii) through which the investigator, the sponsor, VASLCHCS, or VASLCHCS's employees or agents are released from liability for negligence, or appear to be so released.
- (d) Although it is appropriate for consent documents to state that certain specimens or

information may be used for future research purposes, using the word "donation" to characterize the future use of specimens or information for research purposes implies abandonment of rights to the "property" donated and will not be approved by the UU IRB. Whether or not such wording is contained in "the actual informed consent document" is immaterial. All study related documents must be submitted to the IRB for review. Any separate "donation" agreement for future research use of specimens is regarded to be part of the informed consent documentation and must be in compliance with regulatory requirements.

- (e) Informed consent must be obtained prior to initiation of any clinical screening procedures that are performed solely for the purposes of determining eligibility for research.
- (f) When alternatives are proposed, the IRB must determine that the alternative is appropriate under Federal and State law and regulation in the jurisdiction in which the subject will be enrolled and participate. These instances will be handled on a case-by-case basis. In some cases, the IRB may **require** that such alternatives be employed (see below).

(2) **Waiting Periods.** In considering the adequacy of informed consent, permission, and assent procedures, the IRB may require that investigators include a "waiting period" within the process, or employ devices such as audiovisual aids or tests of comprehension. For example, the IRB might determine that obtaining research consent from a surgery subject should be obtained during the usual pre-surgery medical conferences that take place prior to the day of surgery, rather than moments before the surgery begins.

(3) **Consent Monitoring.** In considering the adequacy of informed consent procedures, the UU IRB may require special monitoring of the process by an impartial observer (consent monitor) in order to reduce the possibility of coercion and undue influence.

Such monitoring may be particularly warranted where the research presents significant risks to subjects, or if subjects are likely to have difficulty understanding the information to be provided. Monitoring may also be appropriate as a corrective action where the IRB has identified problems associated with a particular investigator or a research project.

(4) **Advertisements and Recruitment Incentives.** The UU IRB will review advertisements and recruitment incentives associated with the research that it oversees. Advertisements and incentives are directly related to the informed consent process and must be consistent with prohibitions on coercion and undue influence.

Any advertisement to recruit subjects should be limited to the information the prospective subjects, legally authorized representatives, parents, or guardians need to determine eligibility and interest. When appropriately worded, the following items may be included:

- (a) The name and address of the clinical investigator and/or research institution.
- (b) The condition under study and/or the purpose of the research.
- (c) In summary form, the criteria that will be used to determine eligibility for the study.
- (d) A brief list of participation benefits, if any.



- (e) The time or other commitments required of the subjects.
- (f) The location of the research and the person or office to contact for further information.

Recruitment procedures must be designed so that informed consent, permission, and assent are given freely and coercion and undue influence are avoided. In order to evaluate this, the IRB must know who the subjects will be, what incentives are being offered, and the conditions under which the offer will be made.

- (5) **Payments for Research Participation.** The UU IRB will review any proposed payments to research subjects (or their legally authorized representatives) associated with the research that it oversees. Payments may not be of such an amount as to result in coercion or undue influence on the decision to participate or continue participation. Payments may not be provided on a schedule that results in coercion or undue influence on the decision to participate or continue participation.

VA policy (VHA Handbook 1200.5(12)) prohibits paying subjects to participate in research when the research is an integral part of a subject's medical care and when it makes no special demands on the subject beyond those of medical care. However, payment may be permitted, with prior approval of the IRB, in the following circumstances:

- (a) *No direct subject benefit.* When the study to be performed is not intended to directly 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.
- (b) *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 proposed rate.
- (c) *Comparable situations.* In other comparable situations in which, in the opinion of the IRB, payment of patient volunteers is appropriate.
- (d) *Transportation expenses.* When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism.

Investigators who wish to pay research subjects must indicate in their proposal the justification for such payment with reference to the criteria listed and, in addition, must:

- (a) Substantiate that proposed payments are reasonable and commensurate with the expected contributions of the subject;
- (b) State the terms of the subject participation agreement and the amount of payment in the informed consent form; and
- (c) 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.

(d) State in what form (check, cash, gift certificate, etc.) and when payment will be received by the research participant.

The IRB and the R&D Committee shall review all proposals involving the payment of subjects (in excess of reimbursement for travel) in the light of these guidelines. The research office must ensure that such payments to subjects are made from appropriate funds.

(6) **Indemnity and Liability Provisions.** Subjects in VASLCHCS research may not be asked to waive, or appear to waive, any of their legal rights.

e. **Informed Consent Will Be Documented.** In order to approve research, the IRB must determine that informed consent will be documented in writing, unless documentation can be waived under VA regulations, FDA regulations or the Common Rule.

VA regulations at 38 CFR 16.117, HHS regulations at 45 CFR 46.117 and FDA regulations at 21 CFR 50.27 provides two methods for documenting informed consent:

(1) **Long Form (VA Form 10-1086).** Consent may be documented through use of a written document that embodies all of the required elements of informed consent (these elements will be discussed in detail in Chapter 9). Investigators must use VA Form 10-1086 for obtaining documentation of informed consent. The subject (or the subject's legally authorized representative in compliance with all regulatory requirements) must initial each page and sign the document and a copy must be given to the person signing the document. FDA regulations require that the signature be dated; and

(2) **Short Form (Oral Script).** *Not yet approved by UU IRB, but under consideration.* Consent or permission may also be documented through use of a short form document, which states that the elements of informed consent have been presented orally to the subject (or legally authorized representative in compliance with all regulatory requirements). When this method is used:

(a) There must be a witness to the oral presentation.

(b) The IRB must approve a written summary of what is to be presented orally.

(c) Only the short form must be signed by the subject, representative, parent(s), or guardian(s).

(d) The witness must sign both the short form and the summary.

(e) The person actually obtaining consent must sign the summary.

(f) A copy of the summary and the short form will be given to the subject or the legally authorized representative.

FDA regulations require that when a short form is used, both the short form and the written summary must be in the language understandable to the subject.

The IRB should also consider the following when evaluating the documentation for informed consent:

- (1) **Illiterate Subjects.** Illiterate persons may have informed consent or permission information read to them and may "make their mark" in a manner consistent with the laws of the State in which the research is conducted to document their understanding. In this situation, the oral presentation and informed consent process should be witnessed, preferably by an individual not otherwise involved in the research. Both the witness and the person obtaining consent should also sign the informed consent document.
  - (2) **Blind Subjects.** Blind persons may have informed consent or permission information read to them and may "make their mark" in a manner consistent with the laws of the State in which the research is conducted to document their understanding. In this situation, the oral presentation and informed consent process should be witnessed, preferably by an individual not otherwise involved in the research. Both the witness and the person obtaining consent should also sign the informed consent document.
  - (3) **Non-English Speakers.** The UU IRB may require that informed consent conferences include a reliable translator when the prospective subject does not understand the language of the person who is obtaining consent.
    - (a) When a full-length form embodying all required elements is required by the IRB to document consent that form must be written in a language understandable to the subject. IRBs shall require that appropriately translated consent documents be submitted to the IRB for review and approval prior to their use in enrolling subjects. The IRB may utilize expedited Review procedures in approving such documents if the English language consent document has already been approved, and the investigator attests in writing to the accuracy of the translation.
    - (b) When a short-form consent document is used, the short form itself must be written in a language understandable to the subject, although the summary may be in English. The translator who took part in the informed consent conference may serve as the witness.
  - (4) **Witness Signature.** The requirement of a witness name and signature signifies that the witness has observed the subject signing the consent form. The witness should be someone other than the person who obtains informed consent or someone who is not involved in the day-to-day operations of the research study.
  - (5) **Date Stamp Required.** All informed consent documents will have a date stamp indicating the beginning and end of the approval period during which the document may be used to obtain consent. Only the IRB-approved informed consent or permission document can be used for the informed consent or permission process. The investigator is responsible for storing signed informed consent and permission documents for at least five years following the completion of the research.
  - (6) **Original Signed Copy Filed with Subject's Case History.** VA policy requires that the original signed consent document must be filed in the subject's case history (study file), which is maintained by the Principal Investigator. A copy of the signed informed consent must be provided to the Subject or the subject's legal representative. (VHA Handbook 1200.5 Appendix C (3.b)), and a copy must be in the medical record.
- f. **Safety Monitoring Is Adequate.** In order to approve research, the IRB must determine that, where appropriate, the research plan makes adequate provision for monitoring the data to protect

the safety of subjects. For research in which risks are substantial, a detailed description of the data and safety monitoring plan should be submitted to the IRB as part of the proposal. This plan should contain procedures for reporting adverse events.

In general, it is desirable for a Data and Safety Monitoring Board (DSMB) or Data Monitoring Committee (DMC) to be established for research that is blinded, involves multiple sites, targets vulnerable subjects, or employs high-risk interventions. The UU IRB has the authority to require a DSMB/DMC as a condition for approval of research where it determines that such monitoring is needed.

- g. **Privacy and Confidentiality Provisions Are Adequate.** In order to approve research, the UU IRB must determine that, where appropriate, there are adequate provisions to protect the privacy of subjects and the confidentiality of data. (38 CFR 17.33(a) & (f); 38 CFR 17.278; 38 CFR 17.500-571).

It is important to be sure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individual. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research.

VA personnel may obtain and use medical, technical, and administrative records from this or other VA facilities or VA databases for research purposes when in compliance with all VA regulations and Privacy Rules (VHA Handbook 1200.5 (13.b)). Requests for records from other facilities must be approved by the R&D Committee and the Medical Center Director before being submitted to the appropriate Service Director in VA Central Office.

It also is important to protect individually identifiable private information once it has been collected in order to prevent a breach of confidentiality that potentially could harm subjects. When information linked to individuals will be recorded as part of the research design, the UU IRB requires that adequate precautions be taken to safeguard the confidentiality of the information.

Among the available methods for safeguarding confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.

In reviewing confidentiality protections, the IRB will consider the nature, probability, and magnitude of harms that likely would result from a disclosure of collected information outside the research. It will evaluate the effectiveness of proposed anonymizing techniques, coding systems, encryption methods, storage facilities, access limitations, and other relevant factors in determining the adequacy of confidentiality protections.

- (1) **Federal Privacy Act.** Persons not employed by the VA can only access medical and other VA records within the restrictions of the Federal Privacy Act and other statutes. Requests for such documents must be submitted to the Chief Officer, Office of 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 (FOIA) must be handled in accordance with VA FOIA implementing guidelines. (VHA Handbook 1200.5(13.c)).

- (2) **Certificates of Confidentiality.** Where research involves the collection of highly sensitive

information about individually identifiable subjects, the IRB may determine that special protections are needed to protect subjects from the risks of investigative or judicial processes.

In such situations, the UU IRB may require that an investigator obtain a DHHS Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, State, or local civil, criminal, administrative, legislative, or other legal proceedings.

The CoC does not prohibit voluntary disclosure of information by an investigator, such as voluntary reporting to local authorities of child abuse or of a communicable disease. In addition, the CoC does not protect against the release of information to DHHS or FDA for audit purposes. Consequently, that these conditions for release be stated clearly and explicitly in the informed consent.

Information concerning Certificates of Confidentiality can be obtained from the following website:

(a) <http://www.nida.nih.gov/funding/confidentialityfaq.html>

- h. **Additional Safeguards for Vulnerable Subjects.** 38 CFR 16.111(a)(3) requires the IRB must determine that, where appropriate, additional safeguards have been included to protect the rights and welfare of subjects who are likely to be vulnerable to coercion or undue influence, such as children, (45 CFR 46 Subpart D), prisoners (45 CFR 46 Subpart C), pregnant women (45 CFR 46 Subpart B), persons with mental disabilities, or economically or educationally disadvantaged persons. Details about protections for vulnerable subjects are provided in Chapter 15.

To the extent that such subjects are economically dependent upon the VA for medical treatment, suffer from cognitive, affective, or other psychological afflictions, or have substance abuse problems, VA human subjects may be particularly vulnerable to unintended, coercive or undue influences relative to participation in research. Likewise, persons who primarily look to the VA for treatment of their medical problems may not fully understand the implications of research participation, especially when it is offered by someone they consider a provider of clinical care.

Should the UU IRB find that they regularly review research involving such vulnerable subjects, the IRB will include among its reviewers persons who are knowledgeable about and experienced in working with these vulnerable subjects (38 CFR 16.107(a) and 45 CFR 46.107(a)).

- i. **Criteria for Flagging Subjects Medical Record.** VA policy requires that the IRB determine if the subject's medical record (electronic or paper) must be flagged to protect the subject's safety by indicating his/her participation in the study and the source of more information on the study. The UU IRB has delegated this duty to the VASLCHCS R&D RRC Committee. In making this determination, the RRC may consider the type of research (e.g., use of previously collected biological specimens), number of interventions, and risks involved with the research.
- j. **Criteria for Requiring Review More Often Than Annually.** The UU IRB recognizes that protecting the rights and welfare of subjects sometimes requires that research be reviewed more often than annually. For example, when a new intervention is being tested, the risks may not be completely known. The IRB shall monitor the research project closely, and require more frequent review.

The IRB shall consider the following factors in determining the criteria for which studies require more frequent review and what the timeframes generally will be:

- (1) Probability and magnitude of anticipated risks to subjects.
- (2) Likely medical condition of the proposed subjects.
- (3) Overall qualifications of the principal investigator and other members of the research team.
- (4) Specific experience of the principal investigator and other members of the research team in conducting similar research.
- (5) Nature and frequency of adverse events observed in similar research at this and other facilities.
- (6) Vulnerability of the population being studied.
- (7) Other factors that the IRB deems relevant.

In specifying an approval period of less than 1 year, **the IRB may define the period with either a time interval or a maximum number of subjects, i.e.,** after 3 months or after three subjects. OHRP recommends that the minutes clearly reflect these determinations regarding risk and approval period.

- k. **Criteria for Requiring Independent Verification From Sources Other than the Investigator.** The UU IRB recognizes that protecting the rights and welfare of subjects sometimes requires that the IRB verify independently, utilizing sources other than the investigator that no material changes or other problematic events have occurred during the IRB-designated approval period. The IRB will consider the same factors as in item "j" above in determining which studies require such independent verification.

## Chapter 8 - IRB Review: Determinations and Approval Requirements

The IRB has the authority to require certain conditions when it approves research, and investigators have an obligation to ensure that the entire research team follows the determinations of the IRB. These determinations and approval requirements are discussed in this chapter.

- a. **Outcomes of IRB Review.** The UU IRB will notify investigators in writing of its determinations. Except for (oral) acknowledgement (not approval) of emergency, one time use of investigational test articles, all IRB actions must be communicated in writing. All oral acknowledgements are followed by written notification.

IRB actions for initial or continuing review of research include the following:

- (1) **Approved as submitted.** Approved as submitted, with no changes (or no additional changes). The research may proceed.
- (2) **Approved with minor changes.** Approved with minor changes to be reviewed by a designated IRB member. Such minor changes must be clearly delineated by the IRB so the investigator may simply concur with the IRB's stipulations. The research may proceed after the required changes are verified and the protocol approved by the designated IRB member-reviewer. IRB staff and so-called nonvoting members of the IRB may not approve these changes. Such changes require the approval of a voting IRB member.
- (3) **Approved with substantive changes.** Approved with substantive changes to be reviewed by the convened IRB. The research may proceed only after the convened IRB has reviewed and approved the required changes to the research.
- (4) **Tabled.** Deferred pending receipt of additional substantive information. The IRB determines that it lacks sufficient information about the research to proceed with its review. The research may not proceed until the convened IRB has approved a revised application incorporating all necessary information.
- (5) **Disapproved.** The IRB has determined that the research cannot be conducted at VASLCHCS or by its employees or agents.

After formal approval from the IRB, a signed and dated VA Form 10-1223 "Report of Subcommittee on Human Studies" will be forwarded to the VA Research Office.

- b. **Expiration of Approval Period.** VA regulations at 38 CFR 16.109(e) state that the UU IRB is required to conduct substantive and meaningful continuing review of research not less than once per year. Thus, **the IRB approval period for research may extend no more than 365 days after the convened meeting at which the research was last approved** (i.e., approved as submitted or approved with minor changes).

**The regulations permit no grace period and no exceptions to this one-year requirement. Research that continues after the approval period expires is research conducted without IRB approval.**

Consequently, the IRB will automatically suspend the enrollment of new subjects in any ongoing research that does not receive continuing review and approval prior to the end of the stipulated

approval period. Previously enrolled subjects may continue their involvement in suspended research only where the IRB determines that continued involvement is in the best interest of the subjects.

- c. **Suspension or Termination of IRB Approval.** The IRB may vote to suspend or terminate approval of research that is not being conducted in accordance with IRB or regulatory requirements or that has been associated with serious unexpected problems or serious harm to subjects.

Where the IRB Chairperson determines that such action is necessary to protect the rights and welfare of subjects, the IRB Chairperson may require an immediate, temporary suspension of enrollment of new subjects or of continued participation of previously enrolled subjects, pending review of the situation by the convened IRB.

The IRB will notify the principal investigator in writing of such suspensions or terminations and will include a statement of the reasons for the IRB's actions. The investigator will be provided with an opportunity to respond in person or in writing.

- d. **Research Activities in Emergency Situations.** DHHS and VA regulations do not permit research activities to be started, even in an emergency, without prior IRB review and approval. When emergency medical care is initiated without prior IRB review and approval, the patient may not be considered a research subject. Such emergency care may not be claimed as research, nor may any data regarding such care be included in any report of a prospectively conceived research activity, except as required under FDA regulations.

The IRB must be notified in writing within 5 working days of any activities involving the Emergency Use of a Test Article under an FDA Exemption or Exception (see Chapter 12). The IRB will acknowledge such notification in writing but, in accordance with FDA guidance, will not issue any "approval" of the activity.

DHHS regulations at 45 CFR 46.101(i) and FDA regulations at 21 CFR 50.24 include special provisions for IRE review and approval of **planned emergency research** with waiver of the usual informed consent requirements. **VA researchers are not permitted to use these provisions.** To date, the VHA Under Secretary for Health has not exercised the authority under 38 CFR 16.101(i) to permit waivers of informed consent in emergency situations for any research conducted in VA facilities or by VA employees or agents. Therefore, planned emergency research is not presently an option for VASLCHCS researchers. However, VASLCHCS researchers may petition the Under Secretary for Health for a waiver of informed consent in emergency situations.

- e. **Research Involving Data Sets and Repositories.** Although data sets and repositories are discussed in more detail in Chapter 14, issues particularly related to IRB review and approvals are summarized here.

When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information. Of course, use of data from publicly available data sets would still be exempt if the information is not sensitive or not identifiable.

The use of existing data sets requires IRB review when they contain identifiable private information



about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

In making this determination, the UU IRB will first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent. If this is not the case, then the IRB will consider whether it is permissible to waive the usual informed consent requirements in accordance with 45 CFR 46.116(d). Many times, a waiver of consent will be appropriate.

In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities. An alternative to anonymizing data (or making data anonymous) is to maintain the data set as a data repository under the guidelines established by OHRP (see below and refer to Guidance on this topic on the OHRP Website).

(1) **Research Utilizing Data or Tissue Repositories.** Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

VA policy (VA Directive 2000-043, "Banking of Human Research Subjects' Specimens") specifies that human biological specimens, as well as the linked clinical data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, must be maintained at VA approved tissue banks, whether the research is funded or unfunded, and regardless of the funding source.

Repository activities involve three components: (i) the **collectors** of data or tissue samples; (ii) the **repository** storage and data management center; and (iii) the **recipient** investigators.

Under a repository arrangement, the IRB formally oversees all elements of repository activity, setting the conditions for collection, storage, secure maintenance, and sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is not required. (Refer to Guidance on this topic on the OHRP Website.)

Typically, these parameters involve formal, written agreements stipulating these conditions:

- (a) The repository will not release any identifiers to the investigator.
- (b) The investigator will not attempt to recreate identifiers, identify subjects, or contact subjects.
- (c) The investigator will use the data only for the purposes and research specified.
- (d) The investigator will comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.

- (2) **Epidemiology Research.** Epidemiology research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. (See Chapter 14 for additional discussion of epidemiology research.) Epidemiology research may also combine historical research with survey and interview research.

Epidemiology studies often present significant problems regarding both **privacy** and **confidentiality**.

- (a) The UU IRB will first consider privacy issues, and must be satisfied that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB will seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.
- (b) Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB will seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.
- (c) Because epidemiology research typically requires very large numbers of subjects, epidemiology investigators almost always request that the IRB waive the usual requirements for informed consent. In order to approve such a waiver in epidemiology research, the IRB must find and document that the first three criteria at 45 CFR 46.116(d) for a waiver of informed consent have been met; specifically that (a) the research presents no more than minimal risk to subjects; (b) the waiver will not adversely affect the rights and welfare of the subjects; and (c) the research could not practicably be carried out without the waiver. The fourth requirement ("whenever appropriate, the subjects will be provided with additional pertinent information after participation") usually does not apply.
- (3) **Issues in Genetic Research.** Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic information can adversely affect an individual's insurability and employability.

The UU IRB will be particularly careful about approving research that appears to involve only a simple, minimal risk blood draw, but then goes on to include or add a component involving genetic analysis. The addition of the genetic analysis can radically alter the level of risk.

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB will expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained.

- (4) **Family History Research.** Family history research is a common technique used in Bio-Social and Bio-Behavioral Research. Family history research typically involves obtaining information from one family member (called a proband) about other family members.
- (a) It is important to recognize the Federal regulations and the Common Rule include in the

definition of human subject a living individual about whom an investigator obtains "identifiable private information."

- (b) Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information about them.
- (c) The IRB must determine whether family members are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived under the conditions specified at 45 CFR 46.116(d).

- f. **International Research.** All human subject research in which VASLCHCS investigators are involved must comply with all applicable federal regulations for the protection of human subjects in all material respects. This includes research conducted by VASLCHCS investigators in foreign countries.

VA regulations at 38 CFR 16.101(h) and DHHS regulations at 45 CFR 46.101(h) recognize that "the procedures normally followed in the foreign countries may differ from those set forth in this policy." Research may be approved, therefore, if "the procedures prescribed by the [foreign] institution afford protections that are at least equivalent to those provided in this policy." The foreign country's procedures may then be substituted for the procedures required by the federal regulations. Approval of the substitution is to be given by the relevant federal department or agency head after review of the foreign procedures; notice of actions taken on such reviews is to be published in the Federal Register (or elsewhere, as provided for in department or agency procedures). *Note: FDA has not adopted this provision for research that it regulates. All FDA funded research, however, must comply with both DHHS and FDA regulations.*

Investigators should submit the following additional documentation:

- (1) Adequate documentation of prospective host-country ethical review and government approval.
- (2) Copies of the applicable OHRP-approved Human Subject Protection Assurances from international institutions involved in VASLCHCS research (e.g., Federalwide Assurance (FWA) for the Protection of Human Subjects For International (Non-U.S.) Institutions).
- (3) Required current approval letters from the entity responsible for approving the research in the host country.
- (4) Approval period issued by such host-country entities.
- (5) Information relating to the manner of recruiting subjects.
- (6) Information regarding the cultural norms in the host country and how (i) the recruitment of subjects; (ii) consent process including permissions; (iii) any incentives; (iv) confidentiality and privacy issues; and (v) the general conduct of the research would interact with those norms.

The IRB may require confirmation that the informed consent documents for use in other countries provide adequate contact persons in the host county in addition to contacts in the United States.

- g. **Collaborative Department of Defense (DOD) Research.** Research may involve DOD funding or active military personnel, or DOD research may utilize VASLCHCS resources, is also

regulated by the Department of Defense (32 CFR Part 219). Similar to the VA review process, which requires the R&D Committee to review human subject research, DOD also has a second level of review beyond the IRB by a Central Review Specialist/Scientist or committee. When the research involves active military personnel, the UU IRB will be especially careful in reviewing research that involves recording sensitive identifiable information that may be damaging to the subject's employability, since the research records may be subject to review by DOD.

- h. **Compliance with All Applicable State and Local Laws.** All human subject research conducted at VASLCHCS or by VASLCHCS employees or agents on official VA duty time must comply with all applicable in the jurisdiction in which the research takes place. Relevant State and local laws are applicable.

## Chapter 9 - Informed Consent: Required Elements

One overarching requirement of research involving human subjects is that investigators must obtain the informed consent of prospective subjects before they can be included in research. Informed consent presumes two simultaneous concepts: informed decision making and voluntary participation. Prospective subjects must be given sufficient information about the research and its risks and benefits to reach an **informed decision** as to whether they will **voluntarily participate**.

- a. **Required Elements of Informed Consent.** To ensure an effective informed consent process, Department of Veterans Affairs (VA) regulations at 38 CFR 16.116(a), the Common Rule, and FDA regulations mandate the inclusion of eight basic informed consent elements. Six additional elements may be required, depending on the nature of the research. **The UU IRB may require any or all of the six additional elements depending on the nature of the research** (see item "b" below), **as well as any other information it deems warranted to ensure adequate protection of subjects' rights and welfare.**

VHA Under Secretary for Health VA Form 10-1086 is to be used for all VA research.

- (1) **Research Statement (Required Element #1).** Informed consent information must include the following:

- (a) A statement that the study involves research.
- (b) An explanation of the purposes of the research.
- (c) An explanation of the expected duration of subjects' participation.
- (d) A description of what procedures will be followed.
- (e) Identification of any procedures that is experimental.

If the treating physician is also the research investigator, some subjects may not realize they are participating in research, but believe they are just being treated for their condition. By specifying the purpose of the research and describing experimental procedures, it is intended that subjects will be able to recognize the difference between research and treatment.

- (2) **Reasonably Foreseeable Risks or Discomforts (Required Element #2).** Informed consent information must describe any reasonably foreseeable risks or discomforts associated with the research. Risks should be listed in descending order of probability and magnitude (risk of death (even if remote) before risks associated with blood draw, for example).
- (3) **Reasonably Expected Benefits to Subjects or Others (Required Element #3).** Informed consent information must describe any benefits to subjects or to others that may reasonably be expected from the research. However, care must be taken not to overstate the benefits and create an undue influence on subjects. Payment for subject's participation in a research project is not to be considered as a benefit of the research.
- (4) **Appropriate Alternatives (Required Element #4).** Informed consent information must include a disclosure of any appropriate alternative procedures or courses of treatment that may

be advantageous to the subject. Enough detail must be presented so that the subject can understand and appreciate the nature of any alternatives. It is not sufficient simply to state, "the doctor will discuss alternatives to participating."

- (5) **Extent of Confidentiality (Required Element #5).** Informed consent information must describe the extent to which confidentiality of records identifying the subject will be maintained (or not maintained). Research often poses the risk of loss of confidentiality to subjects who participate. Many persons who would not otherwise have access to identifiable, private information about the subject may be involved in the research process. Consent information should describe any procedures that the research team will use to protect subjects' private records. In some research, loss of privacy may be the greatest risk of participation.
- (6) **Compensation or Treatment for Injury (Required Element #6).** Informed consent information for research involving more than minimal risk must include explanations regarding:
  - (a) Whether any compensation is available if injury occurs.
  - (b) In accordance with Federal law, a statement that veteran-subjects shall receive medical care and treatment for injuries suffered as a result of participating in a VA research program. And whether any medical treatments are available if injury occurs.
  - (c) A description of any such compensation or treatments or where more information about them is available.
  - (d) A description of any applicable state law.
- (7) **Contact Information (Required Element #7).** Informed consent information must include details, including telephone numbers, about whom to contact for three specific situations:
  - (a) For answers to questions about the research. The principal investigator and other members of the research team are appropriate contacts for this information.
  - (b) For answers to questions about subjects' rights. The IRB Office or Patient Advocate Office is appropriate contacts for this information.
  - (c) In the event of a research-related injury occurs. Depending upon the nature of the research, the research team, the emergency services department, or the risk management office may serve as appropriate contacts for this information.
- (8) **Voluntary Participation Statement (Required Element #8).** It is particularly important in the VA context for subjects and prospective subjects to understand and have complete confidence that failure to participate will not jeopardize their VA-provided care. Informed consent information must contain clear statements of the following:
  - (a) Participation in the research is voluntary.
  - (b) Refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled.
  - (c) The subject may discontinue participation at any time without penalty or loss of benefits to

which the subject is otherwise entitled.

- b. **Additional Elements Where Appropriate.** Where appropriate, the regulations require that one or more of the following six additional elements are included in the informed consent information:
- (1) **Unforeseeable Risks to Subjects, Embryos, or Fetuses.** Some research involves particular procedures or interventions that may result in unforeseeable risks to subjects, to the embryo, or the fetus (if the subject is or may become pregnant). For research of such a nature, the informed consent information must warn subjects that some risks are currently not known or not foreseeable.
  - (2) **Investigator-Initiated Termination of Participation.** There may be instances that would require investigators to terminate the participation of particular subjects (e.g., subject non-compliance with research, subject not benefiting from research). The informed consent information must specify these circumstances.
  - (3) **Additional Costs.** If subjects must bear any additional costs (transportation, time away from work, health costs, etc.), these must be disclosed in the informed consent information. Any such costs must be consistent with Federal laws concerning veterans' eligibility for medical care and treatment.
  - (4) **Early Withdrawal/Procedures for Termination.** Subjects have the right to withdraw from the research. However, some studies involve medications or procedures that would be dangerous for subjects to discontinue abruptly. For studies of this nature, the informed consent information must provide subjects with knowledge of the consequences affecting a decision to withdraw. In addition, if there are procedures regarding how to withdraw safely from the research, these must also be described. It is not appropriate for research staffs to administer any additional research-oriented questionnaires or interventions that do not affect the safety of subjects who have decided to withdraw.
  - (5) **Significant New Findings.** During the course of research, significant new knowledge or findings about the medication or test article and/or the condition under study may develop. Since the new knowledge or findings may affect the risks or benefits to subjects or subjects' willingness to continue in the research, the informed consent information must detail the procedures for contacting subjects regarding this new information and for affirming their continued participation.
  - (6) **Approximate Number of Subjects.** For certain types of research, the informed consent information should disclose the approximate number of subjects to be enrolled.
- c. **Additional VA-Specific Information.** VA policy (VHA Handbook 1200.5 Appendix C) stipulates that informed consent information include the following elements where appropriate:
- (1) **Payment for Treatment.** Informed consent information must include a statement that veteran-subjects shall 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 co-payments, if so indicated by a means test.
- d. **Payment for Participation.** The informed consent information should include a clear statement describing any payment the subject is to receive for participation, the required conditions for

payment, and the payment schedule. Since VA regulations at 38 CFR 16.116(a)(8), the Common Rule, and FDA regulations all state that subjects may withdraw from research at any time without penalty of loss of benefits to which they are otherwise entitled, completing the research may not be made a condition of payment. For this reason there should be a description of how payment will be prorated and calculated for subjects who withdraw early. (See also, Chapter 7).

- e. **Legally Authorized Representative.** Where consistent with state law, VA policy recognizes as legally authorized representatives (1) persons appointed as health care agents under a Durable Powers of Attorney for Health Care; (2) court appointed guardians; (3) next of kin in the following order: spouse, adult child, parent, and adult sibling. However, VA policy limits the conditions under which the IRB may approve the use of consent from legally authorized representatives. (See also, Chapter 14, item "f" on surrogate consent).
- f. **Guidelines for Conducting an Informed Consent Conversation.** The following information is intended to help investigators and study coordinators conduct informed consent conversations.

Informed consent should not be viewed as a one-time event or discussion with a subject. Rather, informed consent is an ongoing process of communication with the subject by the investigator and the research team.

As a good practice, many investigators and study coordinators first introduce the research with potential subjects in a general fashion, and then set up a time and place to review the intricacies of the research using the informed consent document as a guide. Potential subjects should be given a copy of the informed consent document so they can discuss the research with their family and significant others and develop questions to ask at their next meeting with the research staff. After receiving satisfactory answers to such questions, the subject can sign the informed consent document if he or she wishes to participate. Such a lengthy and detailed enrollment procedure illustrates that obtaining the legally effective informed consent of subjects requires time, diligence, and patience on the part of the research staff and a voluntary, informed decision on the part of the subject.

The context of how, when, and where the investigator obtains the subject's informed consent is important as well. The circumstances, surroundings, and environment of informed consent discussions must provide the subject with an ample opportunity to determine whether or not to participate. The possibility of undue influence or coercion must be minimized. Investigators must be particularly cautious when enrollment of a subject involves a treating clinician asking a patient to enter a research project.

Informed consent information must be presented in language, including vocabulary that is understandable to the subject.

Informed consent must be obtained prior to initiation of any clinical procedures that are performed solely for the purposes of determining eligibility for research.

It is important for investigators to provide the IRB with a description of the proposed consent process and translated consent documents or describes the communication of information in other languages, when required.

- g. **Waiver or Alteration of Informed Consent Requirements: State or Local Public Benefit Programs.** VA regulations at 38 CFR 16.116(c) and the Common Rule permit an IRB to approve



a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document that:

- (1) The activity constitutes a research or demonstration project that 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 or 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; *and*
- (2) The research could not practicably be carried out without the waiver or alteration.

This waiver provision is not applicable to research governed by FDA regulations, and the UU IRB will not approve such alterations or waivers for FDA-regulated research.

- h. **Waiver or Alteration of Informed Consent Requirements: Minimal Risk Research.** VA regulations at 38 CFR 16.116(d) and the Common Rule permit an IRB to approve a consent procedure that eliminates or alters the required elements of informed consent, or to waive the requirement to obtain informed consent altogether. In order to approve such a waiver or alteration, the IRB must find and document 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 practically be carried out without the waiver or alteration; *and*
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

This waiver provision is not applicable to research governed by FDA regulations, and the UU IRB will not approve such alterations or waivers for FDA-regulated research.

## Chapter 10 - Informed Consent: Documentation Requirements

Investigators are usually required to document informed consent using a written consent form signed by the subject or the subject's legally authorized representative and signed by a witness who serves as an impartial observer of the informed consent process. This chapter discusses the documentation requirements and presents the factors involved in obtaining a waiver of these requirements.

- a. **Informed Consent Will Be Documented.** In order to approve research, the IRB must determine that informed consent will be documented in writing, unless documentation can be waived under VA regulations, FDA regulations or the Common Rule.

VA regulations at 38 CFR 16.117, HHS regulations at 45 CFR 46.117 and FDA regulations at 21 CFR 50.27 provides two methods for documenting informed consent:

- (1) **Long Form (VA Form 10-1086).** Consent may be documented through use of a written document that embodies all of the required elements of informed consent (these elements are discussed in detail in Chapter 9). Investigators must use VA Form 10-1086 for all VA funded research. The subject (or the subject's legally authorized representative in compliance with all regulatory requirements) must sign the document and a copy. must be given to the person signing the document. FDA regulations require that the signature be dated; and
- (2) **Short Form (Oral Script). Not yet approved by UU IRB but under consideration..** Consent or permission may also be documented through use of a short form document which states that the elements of informed consent have been presented orally to the subject (or legally authorized representative in compliance with all regulatory requirements). When this method is used:
  - (a) There must be a witness to the oral presentation.
  - (b) The IRB must approve a written summary of what is to be presented orally.
  - (c) Only the short form must be signed by the subject, representative, parent(s), or guardian(s).
  - (d) The witness must sign both the short form and the summary.
  - (e) The person actually obtaining consent must sign the summary.
  - (f) A copy of the summary and the short form will be given to the subject or the legally authorized representative.

FDA regulations require that when a short form is used, both the short form and the written summary must be in the language understandable to the subject.

- b. **Obtaining Consent from Non-English Speakers.** VA regulations at 38 CFR 16.116 and the Common Rule require that informed consent be obtained in language that is understandable to the subject (or the subject's legally authorized representative).

In accordance with these regulations, the UU IRB requires that informed consent discussions include a reliable translator when the prospective subject does not understand the language or the person who is obtaining consent.

Investigators can document informed consent in either of two ways:

- (1) A full-length informed consent document written in language understandable to the subject; or
- (2) A "short-form" consent document in the language of the subject that states the general elements of informed consent.

If investigators use the "short form" to document informed consent, they must also provide subjects with (i) the full-length informed consent document in English, and (ii) a translator who can take part in the oral informed consent conversation to ensure subject understanding and who may serve as the witness. The "short form" consent document written in the subject's language must be signed by the subject (or the subject's legally authorized representative) and the witness. The full-length English consent document must be signed by the witness and the person obtaining consent. The subject must be given copies of both the "short form" consent document and the English consent document.

Whether a full-length or a "short form" consent document is utilized, the UU IRB will require that appropriately translated documents be submitted to the IRB for review and approval prior to their use in enrolling subjects.

It is important for investigators to provide the IRB with a description of the proposed consent process and translated consent documents or describes the communication of information in other languages, when required.

- c. **Waiver of Documentation of Consent.** VA regulations at 38 CFR 16.117(c) and the Common Rule permit an IRB to waive the requirement to obtain written documentation of informed consent. In order to approve such a waiver, the IRB must find and document **either** of the following conditions:

- (1) 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. In this case, each subject will be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern; or
- (2) The research presents no more than minimal risk of harm to subjects and involves procedures or activities for which written consent is not normally required outside of the research context. In cases in which the documentation requirement is waived, the IRB may require the Principal Investigator to provide subjects with a written statement regarding the research.

## Chapter 11 - Investigators' Duty to Report Unanticipated Problems or Adverse Events

VA regulations at 38 CFR 16.103(b)(5), the Common Rule, and FDA regulations at 21 CFR 56.108(b) require that investigators report promptly to the IRB (i) any unanticipated problems in research involving risks to subjects or others; and (ii) any serious or continuing noncompliance with the human subject regulations or the determinations of the IRB; and any protocol deviations (see UU IRB Guidance Document for Protocol Deviations). See Chapter 6 for a discussion of the IRB's reporting responsibilities.

- a. **Investigators' Duty to Report to the Sponsor.** FDA IND regulations require that the investigator report promptly to the Sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)). FDA IDE regulations require that the investigator notify the sponsor of any unanticipated adverse device effect within 10 days (21 CFR 812.150(a)(1)).
- b. **Investigators' Duty to Report to the UU IRB.** Investigators are required to report the following to the IRB by submitting IRB Reporting Adverse Events and Unanticipated Problems.

It is important for investigators to understand that the terms "adverse events" and "unanticipated problems" are defined differently. Although sometimes overlapping in their application, these terms are not synonymous. Any specific "unanticipated problem" may or may not be an "adverse event" and vice versa. However, both must be reported to the IRB.

- (1) **Investigators' Duty to Report Unanticipated Problems.** Investigators are required to report to the IRB **any unanticipated problems involving risks to subjects or others** that occur in research conducted at VASLCHCS facilities or by VASLCHCS's employees or agents.

Note that under DHHS regulations, "unanticipated problem" means any research related event involving risk to anyone associated with the research in any way (including investigators and research assistants) that is not included in the protocol and informed consent document. It includes not only unanticipated adverse events, but also other unanticipated problems (e.g., breeches of confidentiality, equipment malfunctions that may injure the investigator, loss of data that results in the need to enroll additional subjects, thus exposing additional subjects to the risks of the research).

FDA interprets "any unanticipated problems involving risks to human subjects" to mean "...an unexpected adverse experience that is not listed in the labeling for the test article....including an event listed in the labeling ...that differs ...because of greater specificity or severity" (FR 28027).

FDA interprets "...and others" to mean "...persons who are participating in clinical trials under the same or similar protocols or who may be affected by products or procedures developed in those trials" (FR 28027).

- (2) **Investigators' Duty to Report Serious Adverse Events.** Investigators are required to report to the IRB **any serious adverse event** that occurs in research conducted at VASLCHCS facilities or by VASLCHCS's employees or agents.

**A serious adverse event** is defined as any adverse experience occurring that results in any of the following outcomes: death, a life-threatening experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect (21 CFR 312.32(a); 21 CFR 812.3(s)).

- (3) **Investigators' Duty to Report Other Adverse Events.** Investigators are required to report to the sponsor and/or the FDA any adverse event occurring in research conducted at VASLCHCS facilities or by VASLCHCS's employees or agent.
- (4) **Investigators' Duty to Forward Correspondence or Reports of Monitoring or Auditing.** Investigators are required to forward reports or correspondence concerning the monitoring or auditing of their research activities or research sites by sponsors, cooperative research groups, federal agencies, or other external entities to the IRB in a timely fashion.
- (5) **Investigators' Duty to Forward Data and Safety Monitoring Board (DSMB) Reports.** Investigators are required to forward DSMB reports to the IRB in a timely fashion. When DSMBs are employed, IRBs conducting continuing review of research may rely on a current statement from the DSMB indicating that it has reviewed study-wide adverse events, interim findings, and any recent literature that may be relevant to the research, in lieu of requiring that this information be submitted directly to the IRB. Of course, the IRB must still receive and review reports of local, on-site unanticipated problems involving risks to subjects or others and any other information needed to make its continuing review substantive and meaningful.
- (6) **Investigators' Duty to Notify the IRB of Serious or Continuing Noncompliance.** Whether involved in the research or not, all employees and agents of VASLCHCS are required to notify the IRB if they become aware of any serious or continuing noncompliance with human subject regulatory requirements or with the determinations of the IRB.

**Serious** noncompliance is defined as noncompliance that involves greater than minimal risk of harm or discomfort to subjects or others involved in the research.

**Continuing** noncompliance is defined as violation of regulatory requirements or determinations of the IRB that occurs over an extended period.

## Chapter 12 - FDA Regulated Research: Research Involving Drugs, Devices or Biologics

The Food and Drug Administration (FDA) is a component of the U.S. Department of Health and Human Services (DHHS). The FDA's mission is to promote and protect the public health by helping safe and effective products reach the market, and then monitoring these products for continued safety after they are in use.

The FDA regulates clinical investigations (research) conducted on drugs, biologics, devices, diagnostics, and, in some cases, dietary supplements, color additives, and food additives, hereinafter referred to as "FDA regulated test articles." All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

When an FDA regulated test article is used in research being done at the VA or funded by another federal agency, more than one set of regulations may apply. For example, clinical trials involving FDA regulated test articles that are supported by DHHS (e.g., the National Institutes of Health) fall under the jurisdiction of both the FDA and the DHHS Office for Human Research Protections (OHRP). Such trials must comply with the FDA and the DHHS human subject regulations as well as VA regulations. Where regulations differ, IRBs should apply the stricter one.

- a. **Additional VA Requirements for FDA-Regulated Research.** VA policy (VHA Handbook 1200.5) requires that all research comply with the VA human subject regulations, as well as with all applicable regulations and requirements regarding storage and security procedures for investigational agents.

An M.D. must be listed as a Principal Investigator and/or Responsible Investigator for all studies that involve the use of a drug, biologic, or device.

A VA Investigational Drug Information Record (VA Form 10-9012) must be completed by the principal investigator and submitted to R&D RRC for the Research Pharmacist (VHA Handbook 1200.5(14.c)).

Upon approval of the research by the IRB, a Report of Subcommittee on Human Studies (VA Form 10-1223) must be forwarded to the investigator and the R&D RRC to the Research Pharmacist (VHA Handbook 1200.5(14.c)).

Additionally, a signed copy of the Informed Consent Document (VA Form 10-1086) must be sent to Pharmacy Service to document each subject's consent to participate in the study (VHA Handbook 1200.5(14.c)).

When a study involving investigational drugs has been terminated, the PI must inform both the Research Pharmacist and the R&D RRC (VHA Handbook 1200.5(14.d)).

- b. **INDs and IDEs.** New medical products that have not yet been approved for marketing by the FDA require a special status so they can be legally shipped for the purpose of conducting clinical investigations to establish safety and efficacy. New product applications are submitted to FDA for approval of research involving an investigational drug, device, or biologic as follows:

- (1) **An Investigational New Drug (IND)** application is submitted so that an investigation can be

conducted in support of a potential New Drug Application. An investigational new drug (or investigational drug) means a new drug or biological product used in a clinical investigation. An investigational drug must have an IND number before it can be shipped.

(2) **An Investigational Device Exemption (IDE)** supports research to be conducted for a Pre-Market Approval application. Devices that are substantially equivalent to other devices that are legally on the market are called 510(k) devices (see item "f" below) and can be marketed without clinical testing. Not all investigational devices need an IDE.

(3) **A Biologics License Application** is submitted to the FDA to receive approval for research on biological products that would support a Biologics License. Biologics include any virus, therapeutic serum, toxin, antitoxin, or analogous product applicable to the prevention, treatment or cure of human diseases or injuries.

c. **Investigator Responsibilities.** Under FDA regulations, the investigator in a clinical trial is responsible for the conduct of the study and for leading the team of individuals coordinating the study. Each clinical investigator must accept specific responsibilities that include the following:

(1) Conducting the study(ies) in accordance with the relevant, current protocol(s).

(2) Only making changes in a protocol after notifying the sponsor, except when necessary to protect the safety, rights, or welfare of subjects.

(3) Personally conducting or supervising the investigation(s).

(4) Informing subjects that regulated products are being used for investigational purposes.

(5) Ensuring that the requirements for informed consent and IRB review are met.

(6) Reporting adverse experiences to the sponsor.

(7) Understanding the information in the investigator's brochure, including the potential risks and side effects

(8) Maintaining adequate and accurate records and making those records available for inspection.

(9) Promptly reporting to the IRB all changes in the research activity and all unanticipated problems involving risks to human subjects or others

(10) Not making any changes in the research without IRB approval, except where necessary to eliminate apparent immediate hazards to human subjects.

(11) Complying with all other requirements regarding the obligations of clinical investigators and all other pertinent requirements

(12) Ensuring that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting the above commitments.

These responsibilities are specifically listed in the FDA Statement of Investigator (Form 1572), in the

section just above the investigator's signature.

- d. **Sponsor Responsibilities.** The **sponsor** of a clinical investigation initiates and holds the IND or IDE for a clinical investigation, but may not actually conduct the investigation. Although the sponsor is usually a pharmaceutical, biotech, or medical device company, an individual or group of individuals can also be considered a sponsor for an investigation. An investigator is referred to as the **sponsor investigator** when the individual investigator is also the initiator of the clinical investigation.

The responsibilities of sponsors and sponsor-investigators include the following:

- (1) Maintaining the IND, IDE, or Biologics License.
  - (2) Obtaining qualified investigators and monitors.
  - (3) Providing necessary information and training for investigators.
  - (4) Monitoring the investigation.
  - (5) Controlling the investigational agent.
  - (6) Reporting significant adverse events to FDA/investigators.
  - (7) Maintaining and retaining accurate records.
  - (8) Adhering to high ethical standards and good clinical practices.
- e. **IRB Review of Medical Devices.** In accordance with FDA requirements, it is the policy of VASLCHCS that a determination of Significant Risk (SR) or Non-Significant Risk (NSR) for a medical device is made prior to consideration of approval of the medical device study. The Significant Risk vs. Non-Significant Risk determination must be made by the convened IRB. The criteria for approval of device studies are the same as for any FDA-regulated study.

**A Significant Risk (SR) Device** study presents a potential for serious risk to the health, safety, or welfare of a subject and (1) is intended as an implant, or (2) is used in supporting or sustaining human life, or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise prevents impairment of human health. The FDA considers studies of all SR devices to present more than minimal risk; therefore, full IRB review for all studies involving SR devices is necessary. All devices with an IDE number require full Board approval. ***Note:** It is very important to note that the terms "non-significant risk" and "minimal risk" are defined separately, and are not synonymous.*

If the IRB determines, or concurs with the assessment of the sponsor that a device study involves a SR, then it would be governed by the IDE regulations at 21 CFR 812. The determination of the risk status of the device should be based on the proposed use of the device in the investigation. The IRB may review any of the following materials:

- (1) A description of the device.
- (2) Reports of prior investigations conducted with the device.



- (3) The proposed investigational plan.
- (4) A description of subject selection criteria.
- (5) Monitoring procedures.
- (6) The sponsor risk assessment and the rationale used to make the sponsor's risk determination.
- (7) The IRB may also request additional information if necessary from the sponsor or investigator or ask the FDA to provide a risk assessment.

**A No significant Risk (NSR) Device** study is one that does not meet the definition of a SR study. A device study that is deemed to involve a NSR may begin immediately following IRB approval since it would not require the submission of an application to the FDA.

f. **510(k) Devices.** A 510(k) Device is a new device that the FDA agrees is substantially equivalent to a device already on the market. 510(k) devices can be marketed without clinical testing. However, if clinical data are necessary to demonstrate equivalence, any clinical studies must be conducted in compliance with the requirements of the IDE, IRB review and informed consent regulations. Because 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects follow the same requirements (see below).

g. **Radiology Devices and Radioactive Materials.** FDA is responsible for regulating radiology devices and radioactive materials used in healthcare and research. Oversight at the VASLCHCS is handled by the institutional Radiation Safety Committee (RSC).

- (1) **Basic Information.** The research project is only intended to obtain only basic information regarding the metabolism (including kinetics, distribution, and localization) or human physiology, pathophysiology, or biochemistry of a radioactively labeled drug.
- (2) **Safe and Effective.** The radioactive drugs being used are considered safe and effective only after the following determinations are made:
  - (a) The amount of active ingredient or combination of active ingredients to be administered is known not to cause any clinically detectable pharmacological effect in human beings.
  - (b) Under no circumstances does the radiation dose to an adult research subject (either from a single study or cumulatively from a number of studies conducted within 1 year) exceed limits specified by 21 CFR 361.1.
  - (c) The amount of radioactive material to be administered is the smallest radiation dose the subject can practically receive to perform the study without jeopardizing the benefits to be obtained from the study.
  - (d) All radioactive material included in the drug, either as essential material or as a significant contaminant or impurity, was included when total radiation doses and dose commitments were determined.

- (e) Radiation doses from x-ray procedures that are part of the research study (i.e., would not have occurred but for the study) and the possibility of follow-up studies were included in the dose calculations.
- (f) Numerical definitions of dose were based on an absorbed fraction method of radiation absorbed dose calculation, such as the system set forth by the Medical Internal Radiation Dose Committee of the Society of Nuclear Medicine, or the system set forth by the International Commission on Radiological Protection.
- (g) The radiation exposure is justified by the quality of the study and the importance of the information it seeks to obtain.
- (h) Adverse Events must be reported to the RSC.

If all the above determinations cannot be made and fully documented, the radiopharmaceutical may not be classified as "generally recognized as safe and effective," so the RSC may not review and approve the research. An IND may be needed. The IRB has representation from the RSC.

- h. **Investigators' Requirements for Reporting Adverse Events.** The investigators' reporting requirements are provided in more detail in Chapter 11 and are also discussed in Chapter 6. However, for convenience and reference, we summarize the adverse event report requirements for INDs and IDEs here:

(1) **Adverse Events and Reporting Requirements - INDs.** FDA IND regulations require that the clinical investigator report promptly to the sponsor any "adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug. If the adverse effect is alarming, the investigator shall report the adverse effect immediately" (21 CFR 312.64(b)).

- (a) FDA IND regulations require the clinical investigator to notify the sponsor of any adverse effect that may reasonably be regarded as caused by, or probably caused by, the drug.
- (b) Investigators are required to report to the UU IRB:
  - i. Any serious adverse drug effect in VASLCHCS research.
  - ii. Any adverse drug effect reported to the research sponsor or the FDA.
  - iii. Safety reports (or other information concerning adverse events) issued by sponsors, cooperative groups, or DSMBs.
  - iv. Any relevant adverse event information, from any source, that has not already been submitted in accordance with other IRB requirements.

(2) **Adverse Events and Reporting Requirements - IDEs.** FDA IDE regulations require that the investigator notify the sponsor and the IRB of any unanticipated adverse device effect within 10 days.

- (a) The sponsor is required to evaluate the event and report it to the FDA, to all participating investigators, and to all reviewing IRBs within 10 working days of the sponsor's receipt of

the information.

(b) Since 510(k) devices under clinical investigation fall under the IDE regulations, reporting of adverse or unanticipated 510(k) device effects must follow these same requirements.

(c) Investigators are required to report to the UU IRB:

i. Any serious adverse device effect in VASLCHCS research.

ii. Any adverse device effect reported to the research sponsor or the FDA.

iii. Safety reports (or other information concerning adverse events) issued by sponsors, cooperative groups, or DSMBs.

iv. Any relevant adverse event information, from any source, that has not already been submitted in accordance with other IRB requirements.

(3) **Unanticipated Problems.** FDA and DHHS regulations also require reporting of any "unanticipated problems involving risks to subjects or others." It is important for investigators to understand that the terms "unanticipated problems" and "adverse events" are defined differently. Although sometimes overlapping in their application, these terms are not synonymous. Any specific "unanticipated problem" may or may not be an "adverse event" and vice versa. However, both must be reported to the IRB.

i. **Sponsor Reporting Requirements.** Sponsors and **sponsor-investigators** have the following additional reporting responsibilities under FDA regulations:

(1) **Reports to FDA and Investigators (INDs).** FDA IND regulations require that the Sponsor notify the FDA and all participating investigators of any adverse experience associated with the use of a drug or biologic that is both serious and unexpected as soon as possible but in no event later than 15 calendar days after the sponsor determines it to be reportable. The FDA should be notified, by telephone, facsimile, or in writing as soon as possible but in no event later than seven calendar days of the sponsor's receipt of the information of any unexpected fatal or life-threatening experience.

"Serious adverse drug experience" is defined as "any adverse drug experience occurring at any dose that results in any of the following outcomes: death, a life threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect" (21 CFR 312.32(a)).

(2) **Report to FDA, Investigator, and IRB (IDES).** FDA IDE regulations require that the Sponsor is required to evaluate the event and report serious, unexpected adverse device effects to the FDA, to all participating investigators, and to the IRB within 10 working days of the sponsor's receipt of the information.

j. **"Off-label" (Unapproved) Use of FDA-Regulated Products in Medical Practice vs. Research.** The FDA approves the sale, use, and labeling of a product for specific indications (the reason the product is being used - a disease, condition, as a diagnostic tool, etc.). "Off-label" or unapproved use is when the product is used in a way or on a population different from that for which it was approved. The IND regulations do not apply to the use of marketed drugs for

unlabeled indications in the practice of medicine (21 CFR 312.2(d)).

Good **medical practice** and the best interests of the patient require that physicians use legally available, marketed drugs, biologics and devices according to their best knowledge and judgment. If physicians use a product for an indication not included in the approved labeling (i.e., off-label), they have the responsibility to be well informed about the product, to base its use on firm scientific rationale and on sound medical evidence, and to maintain records of the product's use and effects.

The FDA definition of **research** in the IND regulations is as follows: "Clinical investigation" means any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. For the purposes of this part, an experiment is any use of a drug except for the use of a marketed drug in the course of medical practice (21 CFR 312.3(a)). Thus, under the FDA IND regulations, it is possible for one drug given to one person to be considered research.

The off-label use of a marketed drug or biologic in **research** does require IRB review, informed consent and, under some circumstances, may require an IND. To be exempt from the requirements of the IND regulations, all the following must apply (note that includes the requirement of IRB review and informed consent):

- (1) The investigation is not intended to support a new indication for use nor any other significant change in the labeling for the drug.
- (2) The investigation is not intended to support a significant change in the advertising for the product.
- (3) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product.
- (4) The investigation is conducted in compliance with the requirements for institutional review board review and informed consent.
- (5) The investigation is conducted in compliance with the FDA regulations on promoting and charging for investigational drugs (21 CFR 312.7).

Use of an off-label marketed product in research intended to support **a new indication for use, change in labeling or advertising** requires IRB review, informed consent and submission of an IND.

Using an off-label marketed product in research involving a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with its use requires IRB review, informed consent and may also require submission of an IND.

- k. **Expanded Access to Investigational Drugs.** Investigational products are sometimes used for treatment of serious or life-threatening conditions either for a single subject or for a group of subjects. The procedures that have evolved for an investigational new drug (IND) used for these purposes reflect the recognition by the FDA that, when no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses. The following mechanisms expand access to promising therapeutic

agents without compromising the protection afforded to human subjects or the thoroughness and scientific integrity of product development and marketing approval (21 CFR 312.34, 312.35, and 312.83).

- (1) **Treatment IND.** The treatment IND (21 CFR 312.34 and 312.35) is a mechanism for providing eligible subjects with investigational drugs for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments. A treatment IND may be granted after sufficient data have been collected to show that the drug "may be effective" and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment INDs also serve to expand the body of knowledge about the drug. Treatment ND studies require prospective IRB review and informed consent. Four requirements must be satisfied before a treatment IND can be issued:
  - (a) The drug must be intended to treat a serious or immediately life threatening disease.
  - (b) There must be no satisfactory alternative treatment available.
  - (c) The drug must already be under investigation or the drug trials must have been completed.
  - (d) The trial sponsor must be actively pursuing marketing approval.
- (2) **Single Patient Treatment IND.** The Single-Patient Treatment ND is not described in regulations yet, but was added to the law under the FDA Modernization Act (FDAMA) in 1997. From an operational standpoint, the Single-Patient ND must meet the same requirements as a standard IND, and requires IRB review and approval and informed consent.
- (3) **Group C Treatment IND.** Group C drugs are Phase III study drugs that have shown evidence of efficacy in a specific tumor type. Group C drugs are distributed by the National Cancer Institute (NCI) with a Guideline Protocol and an informed consent document. Informed consent is required, and although FDA and NCI permit the use of Group C drugs without local IRB review, VASLCHCS policy normally requires review and approval by the UU IRB. Investigators who are considering use of Group C drugs should contact the IRB Chairperson and/or IRB Administrator for guidance.
- (4) **Orphan Drugs.** The term "orphan drug" refers to a product that treats a rare disease affecting fewer than 200,000 Americans. The treatment use of orphan drugs requires prospective IRB review and approval and informed consent (21 CFR 316.40 and 312.34).
- (5) **Parallel Track Studies.** FDA also permits wider access to promising new drugs for HIV/AIDS related diseases under a "separate access" protocol that "parallels" the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs. These so-called "parallel track" studies require prospective IRB review and informed consent.
- (6) **Open Label Protocol or Open Protocol IND.** These are usually uncontrolled studies, carried out to obtain additional safety data (Phase III studies). They are typically used when the controlled trial has ended and treatment is continued so that the subjects and the controls may continue to receive the benefits of the investigational drug until marketing approval is obtained. These studies require prospective IRB review and informed consent.

1. **Expanded Access to Investigational Devices.** According to statute and FDA regulations, an unapproved medical device may normally only be used in human subjects when the device is under clinical investigation and when used by investigators participating in the clinical trial. FDA recognizes, however, that there may be circumstances under which a health care provider may wish to use an unapproved device to save the life of a patient, to prevent irreversible morbidity or to help a patient suffering from a serious disease or condition for which there exists no alternative therapy. Four main mechanisms are utilized by FDA to make unapproved devices available to patients/physicians faced with circumstances such as those described above. These mechanisms are consistent with the Expanded Access provisions of the FDA Modernization Act of 1997 (Section 561 of the Federal Food, Drug, and Cosmetic Act). The sponsor must agree and FDA must approve the use. Under most circumstances such studies require IRB review and informed consent.
  - (1) **Treatment Use/IDE (21 CFR 812.36).** Treatment use of an investigational device facilitates the availability of promising new devices to desperately ill patients as early as possible before general marketing begins. Such use permits wide access to the device dependent upon patient need. IRB review and approval and informed consent are required. Such use may occur when:
    - (a) The patient has a serious or immediate life-threatening condition.
    - (b) There is no comparable or satisfactory alternative available.
    - (c) The device is under investigation in a controlled trial for the same use (or such trials have been complete).
    - (d) The Sponsor is pursuing marketing approval/clearance.
    - (e) The Sponsor has submitted and the FDA has approved an IDE under 21 CFR 8.12.36.
  - (2) **Single Patient/Small Group Access to Investigational Devices.** Allows access to a device where patient is not eligible for an ongoing clinical trial. The subject must have a serious condition/disease, with no alternative intervention available. Under some conditions, FDA may grant permission even if there is no preexisting IDE.
  - (3) **Continued Access to Investigational Devices.** Allows access to a device while a marketing application is being prepared and reviewed, and can be used to collect additional evidence of safety and effectiveness, as well as to address new questions regarding the investigational device, such as labeling claims. There must be a public health need for the device, as well as preliminary evidence that the device is effective.
  - (4) **Access Under a Formal Protocol.** Access in a controlled rate of enrollment and with no significant safety concerns identified for the proposed indication.
- m. **Gene Transfer Research.** Gene transfer involves the administration of genetic material to alter the biological properties of living cells for therapeutic use. Gene transfer activities in humans are investigational and are regulated by the both the FDA and the National Institutes of Health (NIH) Office of Biotechnology Activities (OBA).

FDA regulations require the submission of an IND for human gene transfer research through the FDA Center for Biologics.

DHHS regulations specify that no individual may be enrolled in human gene transfer research until review has been completed by the NIH Recombinant DNA Advisory Committee (RAC), local Institutional Biosafety Committee (IBC) (VASLCHCS has an MOU with UU to utilize their BSL 3 Facility) approval has been obtained, local IRB approval has been obtained, and the investigator has obtained all other regulatory authorizations from the subject (FR 196, October 10, 2000).

While the RAC is advisory to the Director of the NIH, compliance with its guidelines is mandatory for all investigators at institutions that receive NIH funds for research involving recombinant DNA.

- n. **Emergency Use of a Test Article Without IRB Review.** An exemption under FDA regulations at 21 CFR 56.104(c) permits the emergency use of an investigational drug, device, or biologic on a one-time basis per institution without IRB review and approval.
- (1) **Emergency Use of Drugs.** Emergency use of an investigational new drug occurs when the emergency situation does not allow time for submission of an IND. Use of the drug requires a request to FDA to authorize shipment of the drug for the emergency use. Such authorization is conditioned on the sponsor making an appropriate IND submission as soon as practicable (21 CFR 312.36). The emergency use of an investigational new drug may take place without IRB review and approval, provided that the use is reported to the IRB within 5 working days. Informed consent is required unless the situation is life-threatening, the criteria at 21 CFR 50.23(a) or 50.23(b) have been met, and the IRB is notified within 5 working days.
  - (2) **Emergency Use of Devices.** Emergency use of an unapproved device may occur in an emergency situation when (i) an IDE for the device does not exist, (ii) a physician wants to use a device in a way not approved under an existing IDE, or (iii) when a physician is not an investigator under the existing IDE. The device may be used if (i) the patient has a life-threatening condition that needs immediate treatment, (ii) there is no generally acceptable alternative treatment, and (iii) there is no time to obtain FDA approval. Such uses require as many of the following patient protections as possible (FDA Center for Devices and Radiological Health Guidance on IDE Policies and Procedures, January 20, 1998): (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB chairperson (this concurrence does not constitute IRB approval); (iv) an independent assessment of an uninvolved physician; and (v) authorization from the IDE sponsor (if an IDE exists). Follow-up reports should be provided to the Sponsor if an IDE exists, or to FDA if no IDE exists. Such use is limited to a few patients.

If at all possible, investigators should consult the IRB Chairperson for guidance when considering the emergency use of drugs or medical devices. VA policy requires separate authorization from the Under Secretary for Health for patients outside a research protocol for each such emergency use of a test article without IRB review, as well as the filing of VA Form 10-9012 Investigational Information Drug Record with the Chief of Pharmacy Services.

The following conditions must be met for this type of emergency use:

- (1) A human subject is in a life-threatening situation.
- (2) No standard acceptable treatment is available.
- (3) There is insufficient time to obtain IRB approval.

- (4) The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB.
- (5) Ordinarily, the investigator must obtain the informed consent of the subject for such an emergency use, except as described below.

o. **Emergency Use of a Test Article Without Informed Consent.** An exception under FDA regulations at 21 CFR 50.23 permits the emergency use of an investigational drug, device, or biologic without informed consent where the investigator and an independent physician who is not otherwise participating in the clinical investigation certify in writing all four of the following specific conditions:

- (1) The subject is confronted by a life-threatening situation necessitating the use of the test article.
- (2) Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
- (3) Time is not sufficient to obtain consent from the subject's legally authorized representative.
- (4) No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5 working days. The emergency use must be reported to the IRB within 5 working days. This reporting must not be construed as an approval for the emergency use by the IRB. *Note: This use without prospective IRB approval is not research, but medical treatment, and cannot be counted as research data.*

p. **"Compassionate" or "Humanitarian" Use of a Test Article.** "Compassionate Use" is not a term that appears in the FDA or DHHS regulations or the Common Rule.

For studies involving investigational drugs "Compassionate Use" is often meant to refer to the emergency use situations discussed above. The term does not appear in FDA guidance relating to investigational drugs.

For studies involving investigational devices, compassionate use may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious condition who does not qualify for the trial. Such uses require prior FDA approval of a protocol deviation under 21 CFR 812.35(a). Prior FDA approval for compassionate use should be obtained before the device is used.

On occasion, compassionate use may occur even if there is no IDE for the device. Under this situation, the physician would submit the compassionate use request directly to FDA.

Compassionate use of an unapproved device also requires as many of the following protections as possible: (i) informed consent; (ii) clearance from the institution; (iii) concurrence of the IRB Chairperson (which does not constitute IRB approval); (iv) an independent assessment of an uninvolved physician; and (v) authorization of the IDE sponsor. Follow-up reports should be



provided to the Sponsor. Such use may involve an individual patient or a small group of patients.

If at all possible, investigators should consult the IRB Chairperson for guidance when considering such "compassionate use."

*Note: The above "Compassionate Use" situations should not be confused with the Humanitarian Use Device (HUD) Exemption (see item "q" below).*

- q. **Humanitarian Device Exemptions.** A Humanitarian Use Device (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects fewer than 4,000 individuals in the United States per year. FDA developed this regulation to provide an incentive for the development of devices for use in the treatment or diagnosis of diseases affecting these populations. The regulation provides for the submission of a humanitarian device exemption (HDE) application. An HDE application is not required to contain the results of scientifically valid clinical investigations demonstrating that the device is effective for its intended purpose. The application, however, must contain sufficient information for FDA to determine that the device does not pose an unreasonable or significant risk of illness or injury, and that the probable benefit to health outweighs the risk of injury or illness from its use. The labeling for an HUD must state that the device is a humanitarian use device and that, although the device is authorized by Federal Law, the effectiveness of the device for the specific indication has not been demonstrated.

An approved HDE authorizes marketing of the HUD. However, a HUD may only be used after approval of the convened (full) IRB has been obtained for use of the device at the institution for the FDA approved indication (21 CFR 814.124(a)). After granting initial approval, the IRB may use expedited procedures for conducting continuing review. Informed consent of patients is not required because an HDE provides for marketing approval, so use of the HUD does not constitute research.

- r. **Planned Emergency Research.** An exception under FDA regulations at 21 CFR 50.24 permits planned research in an emergency setting without the informed consent of the subjects. **Planned emergency research is not permitted by the VA.** To date, the Secretary for VA has not exercised the authority under 38 CFR 16.101(i) to permit waivers of informed consent in emergency situations for any research conducted in VA facilities or by VA employees or agents.

## Chapter 13 - Social and Behavioral Research

Social and behavioral research often involves surveys, observational studies, personal interviews, or experimental designs involving exposure to some type of stimulus or intervention. This chapter discusses when a request for exemption or expedited review is appropriate for this type of research so that investigators will know what information to include in their applications to the IRB

- a. **Social and Psychological Harms.** When evaluating behavioral and social science research, the UU IRB carefully examines the research to determine the probability of risk of harm to subjects. The IRB should consider the potential for participants to experience stress, anxiety, guilt, or trauma that can result in genuine psychological harm. The IRB should also consider the risks of criminal or civil liability or other risks that can result in serious social harms, such as damage to financial standing, employability, insurability, or reputation; stigmatization; and damage to social or family relationships.

If information is being collected on living individuals other than the primary "target" subjects, the IRB should consider the risk of harm to those "non-target" individuals, as well. The IRB may require additional protections, study redesign, or the informed consent of "non-target" individuals (unless the requirement for informed consent can be waived).

To mitigate such risks, the UU IRB reviews the proposal for appropriate preventive protections and debriefings, adequate disclosure of risks in the informed consent information, and mechanisms to protect the confidentiality and privacy of persons participating in or affected by the research.

- b. **Privacy and Confidentiality Concerns.** The use of confidential information is an essential element of much social and behavioral research. It is important to ensure that the methods used to identify potential research subjects or to gather information about subjects do not invade the privacy of the individuals. In general, identifiable information may not be obtained from private (non-public) records without the approval of the IRB and the informed consent of the subject. This is the case even for activities intended to identify potential subjects who will later be approached to participate in research. However, there are circumstances that are exempt from the regulations, and circumstances in which the IRB may approve a waiver of the usual informed consent requirements. These have been discussed previously in Chapters 7 and 9, and will also be discussed briefly in following sections of this chapter.

It is also important to ensure that adequate measures are taken to protect individually identifiable private information once it has been collected to prevent a breach of confidentiality that could lead to a loss of privacy and potentially harm subjects.

- c. **Safeguarding Confidentiality.** When information linked to individuals will be recorded as part of the research design, the UU IRB ensures that adequate precautions shall be taken to safeguard the confidentiality of the information. The more sensitive the data being collected, the more important it is for the researcher and the IRB to be familiar with techniques for protecting confidentiality.

IRBs that review research in which the confidentiality of data is a serious issue should have at least one member (or consultant) familiar with the strengths and weaknesses of the different mechanisms available.

When reviewing survey and interview research, the IRB will be aware of the regulatory provision at

38 CFR 16.117(c)(1) for waiving documentation of consent when a signed consent form constitutes the only link between the research and the subjects and would itself be a risk to the subjects (see, Chapters 7 and 9).

Among the available methods for ensuring confidentiality are coding of records, statistical techniques, and physical or computerized methods for maintaining the security of stored data.

VA regulations at 38 CFR 16.116(a)(5), FDA regulations, and the Common Rule require that subjects be informed of the extent to which confidentiality of research records will be maintained.

Federal officials have the right to inspect and copy research records, including consent forms and individual medical records, to ensure compliance with the rules and standards of their programs. FDA requires that information regarding this authority be included on the consent information for all research that it regulates. Identifiable information obtained by Federal officials during such inspections is protected by the provisions of the Privacy Act of 1974.

The UU IRB may require that an investigator obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC). The CoC protects against the involuntary release of sensitive information about individual subjects for use in Federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings. CoCs are discussed in Chapter 9.

- d. **Exempt Research.** Some social and behavioral research is exempt from the requirements of the VA regulations (38 CFR 16.101(b)) and the Common Rule. However, appropriate application of these exemptions requires a relatively sophisticated level of expertise and should not be left to individual investigators. UU IRB policy requires that the IRB Chairperson or IRB Vice-Chairperson review all requests for exemption from IRB Review and must have sufficient information from the investigator to ascertain whether the claimed exemption really applies.

The following exemptions are particularly applicable to social and behavioral research. **These exemptions do not apply to FDA regulated research.**

- (1) **Exempt Research in Educational Settings.** Research conducted in established or commonly accepted educational settings that involves normal educational practices is exempt from VA regulations and the Common Rule in accordance with 38 CFR 16.101(b)(1) and 45 CFR 46.101(b)(1).

This exemption does not apply if the setting is not commonly recognized as an educational one, or if other than normal educational practices are employed. Even if the research is exempt, the investigator has an ethical obligation to ensure that students' rights and welfare are respected.

When educational institutions become engaged in the actual conduct of research, they are required to file an Assurance in accordance with VA regulations at 38 CFR 16.103(a) and the Common Rule. See OHRP guidance.

- (2) **Exempt Research Using Educational Tests (Cognitive, Diagnostic, Aptitude, and Achievement Tests), Survey Procedures, Interview Procedures, or the Observation of Public Behavior.** Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is ordinarily exempt under Federal regulations at 38 CFR 16.101(b)(2) and 45 CFR 46.101(b)(2).

When the subjects are adults, this exemption applies UNLESS: (a) information is recorded in an identifiable manner (either directly or indirectly using codes or other identifying links); AND (b) disclosure of the information would place the subject at risk of criminal or civil liability or be damaging to the subject's financial standing, employability, or reputation. *Note: The research is exempt unless both (a) and (b) apply; i.e., the research is exempt unless the information collected is both identifiable and sensitive, except in the case of children as follows.*

This exemption applies to research involving children, EXCEPT that: (a) research involving survey or interview procedures with children is NOT EXEMPT; and (b) research involving observation of the public behavior of children is NOT EXEMPT if the investigator participates in the actions being observed.

If not exempt under the conditions described above, research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior is exempt where: (a) the subjects are elected or appointed public officials or candidates for public office; or (b) federal statutes require confidentiality without exception. *Note: Condition (b) regarding federal statutes rarely applies. The IRB should consult with ORO and OHRP if it receives an exemption request based on absolute confidentiality under a federal statute.*

If not exempt under the conditions described above, the IRB may often utilize expedited procedures for review and approval of research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or the observation of public behavior. See item "e" below.

(3) **Exempt Research Using Existing Data and Documents.** Social and behavioral research often relies on analysis of existing data or documents. Such research, which is often exempt, was discussed in Chapter 6 and will be discussed further in Chapter 14.

e. **Expedited Review of Behavioral and Social Science Research** that presents no greater than minimal risk to subjects and fits one (or more) of the nine categories specified in the November 9, 1998, Federal Register FR 60364-60367 and FR 6035360356 may be reviewed by the IRB utilizing expedited procedures (see Chapter 6).

The categories discussed below are particularly applicable to social and behavioral research, and include research involving children as well as adult subjects.

(1) **Expedited Review of Research Involving Existing Data and Documents (Expedited Category #5).** Minimal risk research involving materials, (including data, documents, records, or specimens) that have been collected, or will be collected solely for non-research purposes, may be reviewed using expedited procedures. The intent is to define two categories here, each appropriate for expedited review.

- (a) Non-exempt research involving materials that have already been collected (for any previous research or non-research purpose) at the time when the research is proposed.
- (b) Non-exempt research involving materials that will be collected in the future for a non-research purpose.

- (2) **Expedited Review of Research Involving Data from Voice, Video, Digital, or Image Recordings Made for Research Purposes (Expedited Category #6).** The UU IRB may utilize expedited procedures to review research that involves the collection of data from voice, video, digital, or image recordings made for research purposes.
- (3) **Expedited Review of Research Involving Individual or Group Characteristics or Behavior or Research Employing Survey, Interview, Oral History, Focus Group, Program Evaluation, Human Factors Evaluation, or Quality Assurance Methodologies (Expedited Category #7).** The UU IRB may utilize expedited procedures to review the following:
  - (a) Research on individual or group characteristics or behavior, or
  - (b) Research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

This category covers a wide range of non-exempt social and behavioral research activities when they present no greater than minimal risk to subjects. Examples include, but are not limited to, research on perception, cognition, motivation, identification, language, communication, cultural beliefs or practices.

- f. **Research Involving Deception or Withholding of Information.** IRBs reviewing research involving incomplete disclosure or outright deception must apply both common sense and sensitivity to the review. **Deception research** involves psychology research in which the subject is not told, or is misled, about the true purpose of the research, such as in certain studies of group processes, contextual influences on cognition, etc.

Where deception is involved, the UU IRB needs to be satisfied that the deception is necessary and that, when appropriate, the subjects shall be debriefed. (Debriefing may be inappropriate, for example, when the debriefing itself would present an unreasonable risk of harm without a corresponding benefit.) The UU IRB should also make sure that the proposed subject population is suitable.

Deception can only be permitted where the IRB documents that a waiver of the usual informed consent requirements is justified under the criteria present in VA regulations and the Common Rule at 38 CFR 16.116(d). Specifically, the UU IRB must find and document that all four of the following criteria have been satisfied:

- (1) The research presents no more than minimal risk to subjects.
- (2) The waiver or alteration shall not adversely affect the rights and welfare of the subjects.
- (3) The research could not practicably be carried out without the waiver or alteration.
- (4) Where appropriate, the subjects shall be provided with additional pertinent information after participation.

In making the determination to approve the use of deception under a waiver of informed consent, the IRB should consider each criterion in turn, and document specifically (in the minutes of its meeting and/or in the IRB protocol file) how the proposed research satisfies that criterion. **Note:**

*The regulations make no provision for the use of deception in research that poses greater than minimal risks to subjects.*

## Chapter 14 - Research Combining Biomedical and Social & Behavioral Elements

Many studies combine characteristics of behavior and social research with characteristics of biomedical research. There are many interdisciplinary combinations of behavioral and medical research. They often use or create tissue, specimen, or data repositories (banks). Such studies are sometimes referred to as bio-social or bio-behavioral research.

- a. **Prospective Use of Existing Materials.** Prospective studies are designed to observe outcomes or events (e.g., diseases, behavioral outcomes, or physiological responses) that occur subsequent to identifying the targeted group of subjects, proposing the study, and initiating the research.

Prospective studies using materials (data, documents, records or specimens) that will "exist" in the future because they will be collected for some purpose unrelated to the research (e.g., routine clinical care) do **not** qualify for **exemption** under VA regulations at 38 CFR 16.101(b)(4) and the Common Rule because the materials in these studies are not in existence at the time the study is proposed and initiated.

However, IRBs may utilize **expedited procedures** (under expedited category #5, see Chapters 6 and 13) to review research that proposes to use materials (i.e., data, documents, records, or specimens) that will be collected in the future (i.e., after the research has been proposed and initiated) for non-research purposes (e.g., clinical observations, medical treatment, or diagnosis occurring in a non-research context).

- b. **Retrospective Use of Existing Materials.** Retrospective studies involve research conducted by reviewing materials (data, documents, records, or specimens) collected in the past (e.g., medical records, school records, or employment records) and existing at the time the research is proposed and initiated.

Such research may be exempt under VA regulations at 38 CFR 16.101(b)(4) if the information is publicly available or if the information is recorded in such a manner that subjects cannot be identified, either directly or through identifiers linked to the subjects (see, Chapters 6 and 8).

If not exempt, the IRB may review such research utilizing expedited procedures, provided that the research involves no more than minimal risk to subjects (see, Chapter 6).

However, retrospective studies using existing materials occasionally entail significant, greater than minimal risks and require review by the convened IRB (e.g., where the research reveals previously undisclosed illegal drug use and the expedited review had concerns about invasion of subjects' privacy and/or the adequacy of confidentiality protections proposed by the investigators).

- c. **Research Utilizing Large Existing Data Sets.** Biosocial and bio-behavioral research often involves the use of large, existing data sets.

When the data sets are publicly available (i.e., available to the general public, with or without charge), their use is exempt, even if they contain sensitive, identifiable information (see Chapter 8). Of course, use of data from publicly available data sets would still be exempt if the information is not sensitive or not identifiable.

The use of large, existing data sets requires IRB review when they contain identifiable private information about living individuals. In such cases, the IRB must determine whether the information can be used without additional informed consent from the subjects.

In making this determination, the IRB should first examine the conditions of informed consent under which the data were originally obtained. It may be that the proposed research is permissible under the original terms of consent.

If this is not the case, then the IRB should consider whether it is permissible to waive the usual informed consent requirements in accordance with 38 CFR 16.116(d). Many times, a waiver of consent will be appropriate.

In other cases, the IRB may determine that the research can proceed only if the investigator obtains and uses "anonymized" data. Under this scenario, codes and other identifiers are permanently removed from the data set before the data are sent to the investigator, and the removal is accomplished in such a manner that neither the investigator nor the source maintaining the data set can re-establish subjects' identities.

An alternative to anonymizing data is to maintain the data set as a data repository under the guidelines established by the Office for Human Research Protections (OHRP) and VA.

- d. **Research Using Data or Tissue Banks (also called Repositories).** Human data repositories collect, store, and distribute identifiable information about individual persons for research purposes. Human tissue repositories collect, store, and distribute identifiable human tissue materials for research purposes.

VA policy (VA Directive 2000-043, "Banking of Human Research Subjects' Specimens") specifies that human biological specimens, as well as the linked clinical data collected as part of research projects conducted by VA investigators in VA facilities or approved off-site locations, must be maintained at VA-approved tissue banks, whether the research is funded or unfunded, and regardless of the funding source.

Tissue Bank activities involve three components: (a) the **collectors** of data or tissue samples; (b) the **bank/repository** storage and data management center; and (c) the **recipient** investigators. Under a repository arrangement, an IRB formally oversees all elements of repository activity, setting the conditions for collection, secure storage, maintenance, and appropriate sharing of the data and/or tissues with external investigators. Specifically, the IRB determines the parameters for sharing data and/or tissues (which are identifiable within the repository) in a manner such that additional informed consent of subjects is, or is not, required.

Typically, these parameters involve formal, written agreements stipulating conditions as follows:

- (1) The repository shall not release any identifiers to the investigator.
- (2) The investigator shall not attempt to recreate identifiers, identify subjects, or contact subjects.
- (3) The investigator shall use the data only for the purposes and research specified.

The investigator shall comply with any conditions determined by the repository IRB to be appropriate for the protection of subjects.



- e. **Epidemiological Research.** Epidemiological research often makes use of sensitive, individually identifiable, private information (usually obtained from medical or other private records), and links this information with additional information obtained from other public or private records, such as employment, insurance, or police records. Epidemiological research may also combine historical research with survey and interview research.

Epidemiological studies often present significant problems regarding both **privacy** and **confidentiality**.

The IRB must first consider privacy issues, and must satisfy itself that the research does not constitute an unwarranted invasion of the subjects' privacy. In doing so, the IRB shall seek to establish that the investigator has legitimate access to any identifiable information that is to be utilized. For example, if State disease registry information is to be utilized, the IRB will need to examine State law relative to the legitimate release of such information for research.

Once the IRB's privacy concerns have been resolved, the IRB will examine mechanisms for maintaining the confidentiality of data collected. The IRB shall seek to establish that confidentiality protections are appropriate to the nature and sensitivity of the information that has been obtained.

Because epidemiological research typically requires large numbers of subjects, investigators almost always request that the IRB waive the usual requirements for informed consent. To approve such a waiver in epidemiological research, the IRB must find and document that the criteria for a waiver of informed consent have been met (38 CFR 16.116(d); specifically that:

- (1) The research presents no more than minimal risk to subjects.
- (2) The waiver will not adversely affect the rights and welfare of the subjects.
- (3) The research could not practicably be carried out without the waiver.
- (4) Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

- f. **Issues in Genetic Research.** Information obtained through genetic research may have serious repercussions for the subject or the subject's family members. Genetic studies that generate information about subjects' personal health risks can provoke anxiety and confusion, damage familial relationships, and compromise the subjects' insurability and employment opportunities. For many genetic research protocols, these psychosocial risks can be significant enough to warrant careful IRB review and discussion. Those genetic studies limited to the collection of family history information and blood drawing should not automatically be classified as "minimal risk" studies qualifying for expedited IRB review. The addition of the genetic analysis can radically alter the level of risk.

The protection of private information gathered for and resulting from genetic research is a major concern. The IRB should expect the investigator to describe in detail how individual privacy will be protected and how the confidentiality of obtained information will be maintained.

- g. **Family History Research.** Family history research is a common technique used in bio-social and bio-behavioral research. Family history research typically involves obtaining information from one

family member (called a proband) about other family members (third parties).

It is important to recognize the VA regulations at 38 CFR 16.102 (f)(2) and the Common Rule include in the definition of human subject a living individual about whom an investigator obtains "identifiable private information."

Thus, the family members identified and described by the proband may be human subjects under the regulations if the investigators obtain identifiable private information about them.

IRBs must determine whether family members (third parties) are human subjects in such research, and if so, consider the possible risks involved, and determine whether their informed consent is required or can be waived (see Chapter 10) under the conditions specified at 38 CFR 16.116(d). There is not total consensus in the available guidance on this issue. OHRP representatives have advised that "third parties" about whom identifiable and private information is collected in the course of research are human subjects. Confidentiality is a major concern in determining if minimal risk is involved. IRB's can consider if informed consent from third parties can be waived in accordance with Section 116 and if so, document that in the IRB minutes. In most cases waiver of consent may be appropriate.

- h. **Research Involving Potentially Addictive Substances.** Research involving potentially addictive substances often involves the use of what may be termed "abuse liable" substances. Abuse-labile substances are pharmacological substances that have the potential for creating abusive dependency. Abuse-labile substances can include both legal and illicit drugs. The following are among the issues that the IRB should consider when reviewing research involving potentially addictive substances:
- (1) When this type of research is proposed, the IRB must consider the subjects' capacity to provide continuous informed consent, ensuring that subjects are competent and are not coerced.
  - (2) If such research involves subjects that are institutionalized, the subjects' ability to exercise autonomy could be impaired.
  - (3) The IRB must also consider the requirements for equitable selection of subjects and protections for maintaining confidentiality, as such a population may be at risk for being discriminated against, or over-selected.
  - (4) The IRB must be sensitive to the ethical context of the research, in that there may be moral dilemmas associated with the use of placebos, or in cases where addicts are presented with alcohol and/or drugs.
  - (5) It is critical that the IRB focus on the considerations of risk and benefit of such research.

## Chapter 15 - Potentially Vulnerable Subject Groups

Investigators must give special consideration to protecting the welfare of particularly vulnerable subjects, such as children, prisoners, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

Because veterans have a history of obeying orders and making sacrifices, and because some veterans may not have access to other health care, some might consider veterans a potentially vulnerable population.

- a. **Elements to Consider in Conducting Research Involving Vulnerable Subjects.** IRBs must pay special attention to specific elements of the research plan when reviewing research involving vulnerable subjects.
  - (1) Strategic issues include inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
  - (2) The IRB should carefully consider group characteristics, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable subjects.
  - (3) Investigators should not be permitted to over-select or exclude certain groups based on perceived limitations or complexities associated with those groups. For example, it is not appropriate to target prisoners as research subjects merely because they are a readily available "captive" population.
  - (4) IRBs must be knowledgeable about applicable state or local laws that bear on the decision-making abilities of potentially vulnerable populations. State statutes often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.
  - (5) Just as in providing medical care, research studies that plan to involve any potentially vulnerable populations must have adequate procedures in place for assessing and ensuring subjects' capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable subjects, the IRB shall look to see that such procedures are a part of the research plan. In certain instances, it may be possible for researchers to enhance understanding for potentially vulnerable subjects. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a subject advocate, interpreter for hearing-impaired subjects, translation of informed consent forms into languages the subjects understand, and reading the consent form to subjects slowly and ensuring their understanding paragraph by paragraph.
  - (6) The IRB may require additional safeguards to protect potentially vulnerable populations. For instance, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

- b. **Research Involving Pregnant Women, Human Fetuses and Neonates.** DHHS regulations at 45 CFR Part 46, Subpart B detail special protections for research involving pregnant women, human fetuses, and neonates. Under these regulations, IRBs are required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent. In general, Subpart B requires that research involving pregnant women and fetuses should involve the least possible risk. The regulations set out specific categories, each with their own requirements and IRB determinations, for research involving pregnant women, human fetuses and neonates.
- c. **Research Involving Prisoners.** DHHS regulations at 45 CFR Part 46, Subpart C detail special protections for research involving prisoners, who due to their incarceration, may have a limited ability to make truly voluntary and uncoerced decisions about whether or not to participate as subjects in research. OHRP discourages expedited review of any research involving prisoners as participants.

A prisoner is defined as any individual involuntarily confined or detained in a penal institution. In order to consider research involving prisoners, the IRB must:

- (1) Have a majority of its members not otherwise associated with the prison.
- (2) Include a prisoner or a prisoner advocate, who can adequately represent the interests of the prisoners, unless the research has already been reviewed by an IRB that included a prisoner advocate.

The IRB should be promptly notified if the investigator becomes aware that a research subject has been incarcerated. The regulations set out specific categories and IRB determinations for research involving prisoners.

- d. **Research Involving Children.** The VA is authorized to care for veterans and to conduct research that enhances the quality of health care delivery to veterans and is not authorized to care for the offspring of veterans. VA policy stipulates that children cannot be included in VA-approved research unless a waiver has been granted by the Chief Research and Development Officer (VA Directive 2001-028, dated April 27, 2001).

DHHS regulations at 45 CFR 46, Subpart D require special protections for research involving children. Under the regulations, **children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.** There are three main issues to consider when reviewing research involving children:

- (1) Risk-benefit analysis.
- (2) Parental permission.
- (3) Assent of the child.

Applicable state laws.

- e. **Research Involving Decisionally Impaired Subjects.** Decisionally impaired persons are individuals who have a diminished capacity for judgment and reasoning due to a psychiatric,

organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals who may be considered decision ally impaired, with limited decision-making ability, are individuals under the influence of or dependent on drugs or alcohol, those suffering from degenerative diseases affecting the brain, terminally ill patients, and persons with severely disabling physical handicaps.

There are no regulations specific to research involving cognitively impaired persons. However, there are specific VA policies that require certain findings to be made before persons incompetent to consent may be enrolled in research with the permission of a surrogate.

In all cases, investigators should take special care to consider issues such as the selection of subjects, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. IRB decisions will be made with the utmost deference to the ethical principles underlying human subject's research as set forth in the Belmont Report. Capacity will be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. In cases where research involving cognitively impaired individuals is approved, the IRB will require additional safeguards (e.g., involvement of subject advocates, independent monitoring, formal capacity assessment, waiting periods) as part of the research plan to protect participants.

f. **Surrogate Permission with Subjects Judged Incompetent to Consent.** The VA Cooperative Studies Program Guidance limits the conditions under which consent from legally authorized representatives (i.e., surrogate consent) can be obtained in lieu of consent from the subject. Where consistent with state law, VA policy (VHA Handbook 1200.5(11)) recognizes as legally authorized representatives:

- (1) Durable Powers of Attorney for Health Care. Persons appointed as health care agents under a Durable Powers of Attorney for Health Care (DPAHC).
- (2) Court appointed guardians.
- (3) Next of kin in the following order: spouse, adult child, parent, and adult sibling.

Surrogate consent may be used only when the prospective subject is incompetent as determined by two VA physicians, after appropriate medical evaluation, and there is little or no likelihood that the subject will regain competence within a reasonable period of time, or as established by legal determination. This definition of incompetence is not limited to the legal definition but may also be a clinical judgment that a person lacks the capacity to understand the circumstances of participating in research and to make an autonomous decision to take part.

Before incompetent persons may be involved in any VA research, the IRB must find and document in writing that the proposed research meets all of the following conditions:

- (1) **Only incompetent persons are suitable.** Competent persons are not suitable for the proposed research. The investigator must demonstrate that there is compelling reason to include incompetent persons as subjects. Incompetent persons must not be involved as subjects simply because they are readily available.
- (2) **Favorable Risk/Benefit Ratio.** The proposed research entails no significant risks, or if the research presents risk of harm, there must at least be a greater probability of direct benefit to the subject than of harm.

(3) **No Resistance.** Subjects do not resist participating. Under no circumstances may subjects be forced or coerced into participating.

(4) **Well-Informed Representatives.** Procedures have been devised to ensure that subjects' representatives are well informed regarding their roles and obligations to protect the rights and welfare of the subjects they represent. Representatives must be informed in writing 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 is in the subject's best interests.

- g. **Research Involving Other Potentially Vulnerable Adult Subjects.** Employees, students, and trainees in the VA Medical Center should also be considered vulnerable subjects. Thus, the IRB should uphold the same standards in approving research involving these groups as other vulnerable subject's research.

The context of the research is an important consideration for IRBs to have in mind when reviewing research that involves other potentially vulnerable subjects. Research involving homeless persons, members of particular minority groups, or the economically or educationally disadvantaged pose significant challenges. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of subjects, and IRBs must take such considerations into account. Nevertheless, research involving these subjects is socially important for understanding and eventually improving adverse health in these populations.

- h. **Human Fetal Tissue Transplantation Research.** Public Law 103-43 governs human fetal tissue transplantation research supported by DHHS. Investigators proposing to conduct fetal tissue transplantation research should consult the provisions of this law and the UU IRB Office.
- i. **Research Involving Deceased Persons.** Research involving deceased persons is not covered by the VA or FDA human subject regulations or the Common Rule. However, such research may be covered under applicable state law.

## Chapter 16 - Education and Credentialing Requirements for Personnel Involved in Human Subject Research

- a. **Education in the Protection of Human Research Subjects.** VASLCHCS is required under its OHRP-approved FWA to have a plan to provide education about human subject protections for research investigators and IRB members and staff.

Additionally, VA policy requires that investigators complete human subject protection education (see VHA Handbook 12005(10.a)).

VA policy requires that all investigators complete annual continuing education as determined by the Office of Research Development (Deputy Under Secretary for Health, Memorandum "Research Requirements," March 6, 2003.).

- b. **VA Credentialing Requirements.** Credentialing is a formal, systematic process of verifying, screening, and evaluating qualifications and other credentials that include education, licensure, relevant training and experience, current competence and health status

Generally, all individuals involved in human subject research must be credentialed.

- (1) *Licensed Independent Practitioners (LIPs)* are individuals permitted by law and their facility to provide patient care services independently, i.e., without supervision or direction, within the scope of the individual's license and in accordance with individually granted clinical privileges. LIPs will complete the credentialing process through VetPro or its paper equivalent. VetPro identify that the LIP has been credential for the purpose of research. (Please contact the Research Service for assistance).
- (2) *Research Staff who do not qualify as LIPs* must provide the Research Service with the following: (i) dated copy of CV/Resume, if available, (ii) copy of current professional license, if applicable, (iii) education verification form. Additionally, the Principal Investigator will provide a Scope of Practice for each member of his research team. (Please contact the Research Service for assistance).

Individuals, including those from affiliated institutions, who satisfy any one of the following criteria must complete the credentialing process as described above:

- (1) Hold a VA paid appointment.
- (2) Perform or conduct any part of the research at this facility (VASLCHCS and associated CBOC's). Additionally, study staffs (performing research duties at this facility) that do not have a VA paid appointment must receive a VA WOC appointment.

The following individuals do **not** need to be credentialed at VASLCHCS:

- (1) Administrative staff.
- (2) Co-investigators based at an affiliate or other outside institution and who do not come to the VA or interact with VA research participants.
- (3) Co-investigators based at another VA facility.

(4) Affiliated or other outside-based biostatisticians.

(5) Affiliated or other outside-based lab technicians.



## Chapter 17 - Managing Conflicts of Interest

Conflict of Interest can be defined as any situation in which financial or personal obligations may compromise or present the appearance of compromising an individual's or group's professional judgment in conducting, reviewing, or reporting research.

Research personnel, IRB members, IRB Chairpersons, managers in the VA Medical Center (VAMC) Research and Development Office, the Institutional Official, and research sponsors may all have certain conflicts of interest. Such conflicts of interest may arise because of the intellectual property involved in many research discoveries or industry-academic partnerships, from financial incentives many pharmaceutical or biotech companies offer researchers or physicians for conducting trials or enrolling subjects, or due to particular role relationships within the governance structure of particular institutions.

- a. **Research Personnel.** For researchers, financial or other incentives may negatively impact the collection, analysis and interpretation of data, scientific objectivity and integrity, and ultimately the public trust in the research enterprise. In addition, if also the treating physician, a researcher may unwittingly exert coercion or undue influence on patients to participate in research (VASLCHCS Station Policy Conflict of Interest relating to all research personnel is currently being drafted).
- b. **VA Regulations and the Common Rule.** The VA human subject regulations at (38 CFR 16.107(e)), the Common Rule, and FDA prohibit IRB members, chairs, or staff who have a conflicting interest from participating in the IRB's initial or continuing review of research.

Such conflicts must be disclosed, and the IRB member, chairperson, or staff member must not take part in the discussion or voting of such research, except to answer questions from the IRE.

IRBs may consider any matter that raises the possibility of coercion or undue influence in the consent process. The existence of an investigator conflict of interest would fall within this category.

As a matter of policy, VASLCHCS requires disclosure of any potential conflicts of interest to appropriate facility officials or committees established for this purpose. Adherence to disclosure requirements is a routine condition for IRB approval of research.

- c. **FDA Requirements.** The FDA requires a sponsor in a marketing application of any drug, device, or biologic to submit certain information on financial interests and arrangements of clinical investigators conducting studies to FDA. The following financial arrangements must be disclosed:
  - (1) Any relationship between the study outcome and the value of the compensation made to the investigator.
  - (2) The investigator's proprietary interest in the studied product t, including but not limited to a patent, trademark, copyright or licensing agreement.
  - (3) Any equity interest in the study sponsor, ownership interest, stock options, or other financial interest.
  - (4) Any equity interest in a publicly held company that exceeds \$50,000 in value.

(5) Significant payment of another type, which has a cumulative monetary value of \$15,000 or more, made by the sponsors to the investigator(s).

- d. **Department of Health and Human Services Public Health Service (DHHS-PHS) Requirements for Grantee Institutions.** DHHS requires that PHS grantee institutions have a written policy and guidelines on conflicts of interest.

A designated institutional official is responsible for reviewing all financial disclosures, and determining if a conflict of interest exists. If one exists, the Institutional Official must determine what actions should be taken to manage, reduce, or eliminate the conflicting interest. IRB SOPs should include a reference identifying the person designated. At this facility, the designated institutional conflict of interest administrator is the Research Compliance Officer.

The PHS requirements call for grantee institutions to:

- (1) Maintain a written, enforced policy on conflicts of interest
- (2) Review all financial disclosure statements (listings of significant financial interests for investigators and immediate family members) for all investigators participating in PHS-funded research
- (3) Report to PHS the existence of a conflicting interest found by the institution and ensure that it has been managed

Under this regulation, an "Investigator" means the principal investigator and any other person who is responsible for the design, conduct, or reporting of the research. For purposes of determining financial interests, the Investigator's interests include those of his/her spouse and dependent children.

**"Significant financial interest"** means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). Financial interests which are subject to reporting for any given research proposal include those which would reasonably appear to be affected by the specific research proposed; and/or are interests in entities whose financial interests would reasonably appear to be affected by the research.

"Significant financial interest" does **not** include:

- (1) Salary, royalties, or other remuneration from the applicant institution.
- (2) Any ownership interests in the institution, if the institution is an applicant under the PHS Small Business Innovation Research Program.
- (3) Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities.
- (4) Income from service on advisory committees or review panels for public or nonprofit entities.
- (5) An equity interest that when aggregated for the Investigator and the Investigator's spouse and

dependent children, meets both of the following tests: (a) Does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and (b) does not represent more than a five percent ownership interest in any single entity.

- (6) Salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over the next twelve months, are not expected to exceed \$10,000.

Examples of **conditions or restrictions** that might be imposed to manage conflicts of interest include, but are not limited to:

- (1) Public disclosure of significant financial interests.
- (2) Monitoring of research by independent reviewers.
- (3) Modification of the research plan.
- (4) Disqualification from participation in all or a portion of the research funded.
- (5) Divestiture of significant financial interests.
- (6) Severance of relationships that create actual or potential conflicts.

Investigators and study team personnel will submit conflict of interest disclosures via the Research Service which will be forwarded to the research conflict of interest administrator.

- e. **The Disclosure Process.** As one method of preventing, monitoring, managing, and resolving conflicts of interest, this facility requires full disclosure of conflicts of interest by investigators and study team personnel.

Full disclosure of conflicting information demonstrates good faith and protects the integrity of the research and the reputation of the institution. Disclosure is initially made to the R&D and the IRB. Annual disclosures are reviewed by the IRB at continuing review.

Where appropriate, and as determined by the IRB and/or the Conflict of Interest Administrator, disclosure to the human subjects involved in the research may be warranted via the informed consent document.

## Chapter 18 - How to Submit Materials to the IRB

Before VASLCHCS research may be initiated, the research must receive approval by both the UU IRB and the R&D Committee. As described in earlier chapters, the VASLCHCS may require additional review by other VAMC committees. Accordingly, the initial review and approval process usually takes longer than 6 weeks due in part to the meeting schedules of the relevant committees. This chapter is intended to provide investigators with an overview of the review and approval process.

*Note: Please be aware that IRB review procedures should not be confused with grant review procedures. The IRB is not involved in competitively ranking you.*

### a. Review of New Research Projects.

- (1) **PI Submits new study to IRB electronic system. Research Compliance Officer (RCO) adds to next agenda of Research Review Committee (RRC) and requests assurance statement, conflict of interest statement and various other statements required of individual studies (pharmacy donation, 1572, 9012, nursing use and request to review forms for the PROMISE system). The PI submits Request to Review Research Proposal to the Research Office (with all requested attachments) for all new protocols to be conducted at VASLCHCS or by VASLCHCS employees or agents. All IRB forms are collected from the IRB electronic submission system. The Request to Review form is used to process the new study through the R&D Committee reviews.**
  - (a) **R&D Committee Review.** The R&D Committee review focuses on assessing the scientific and ethical quality of the research and the investigator's qualifications. The R&D Committee also recommends the distribution of R&D funds, space, personnel, equipment, supplies, and other common resources; and reviews and approves R&D budgetary request of the facility. The R&D and its subcommittees ensure proper resources for the complete protection of human subjects. The R&D Committee meets monthly. The R&D and the IRB Review may occur simultaneously. Full approval from the R&D will not be forwarded prior to IRB approval.
  - (b) **IRB Review** -The IRB conducts its initial review upon receipt of the application from the PI. For information regarding the criteria for IRB review, please refer to [www.utah.edu/irb](http://www.utah.edu/irb) for all forms and instructions.
  - (c) **Subcommittee on Research Safety Review** - The Subcommittee on Research Safety meets monthly and assesses any biosafety issue that is being carried out in the protocol. The review by the Subcommittee on Research Safety focuses on the storage, use and disposal of chemicals, radioisotopes, microbial agents, rDNA, human tissues/specimens, biological toxins, non-microbial agents, and physical agents being utilized.
- (2) **PI Submits Research to Radiation Safety Committee. Investigators** conducting research involving the use of ionizing radiation exposure must submit their study directly to the radiation safety committee for review and approval using the Application for Human Subject Research Involving Ionizing Radiation Exposure.

**For all VA protocols, VA Form 10-1223 will be submitted to the IRB for completion and signature by the IRB for completion and signature by the IRB chair or designee. Completed form must be returned to the Research Service prior to R&D full committee approval.**