

August 28, 2008

## HUMAN RESEARCH PROTECTION PROGRAM

**1. PURPOSE:** The purpose of this policy memorandum is to describe the South Texas Veterans Health Care System (STVHCS) Human Research Protection Program (HRPP) as a complete entity. This document describes the varied and diverse components of the STVHCS HRPP. Other documents that provide more detailed description of aspects of the HRPP are referenced in this document.

**2. POLICY:** The STVHCS, as a Department of Veterans Affairs (VA) health care system, will maintain a human research protection program (HRPP) to adhere to all regulations and directives related to the protection of human subjects in research as required by the VA and all other responsible Federal agencies. All individuals involved in the HRPP must understand and apply their obligation to protect the rights and welfare of human research subjects.

**a. VISION FOR RESEARCH:** The STVHCS aspires to discover knowledge, develop VA researchers and health care leaders, and create innovations that advance health care for our veterans and the nation.

**b. Definitions :**

(1) **Adverse Event (AE) in Research.** An AE in research is defined for purposes of this policy as any untoward occurrence (physical, psychological, social, or economic) in a human subject participating in research. An AE in research can be any unfavorable or unintended event including abnormal laboratory finding, symptom, disease, or death associated with the research or the use of a medical investigational test article. An AE in research may occur even in the absence of any error or protocol deviation, and does not necessarily have to be caused by any identifiable aspect of the research.

(2) **Continuing Review:** Periodic review by the Institutional Review Board (IRB) and R&D Committee of active research for the purpose of re-approving, requiring modifications, disapproving, terminating or suspending the study. Continuing review must occur at least annually, or as determined by the IRB.

(3) c. **Federalwide Assurance (FWA):** An agreement or contract between the institution and Office of Human Research Protections (OHRP), on behalf of the Secretary, Department of Health and Human Services (DHHS), stipulating the method(s) by which the organization will protect the welfare of research subjects in accordance with the regulations. The Assurance, approval of which is a condition of receipt of DHHS support for research involving human subjects, spells out the organization's responsibilities for meeting the requirements of 45 CFR 46. All VA facilities conducting human research are required to maintain an FWA.

(4) **Food and Drug Administration (FDA):** The federal agency within the Department of Health and Human Services that promotes public health by assuring the safety, efficacy, and security of human and veterinary drugs, biological products, medical devices, our nation's food supply, cosmetics, and products that emit radiation.

(5) **Food and Drug Administration (FDA) Regulated Activity:** An activity is FDA regulated when it meets the FDA definition of research, e.g. involves the use of a drug (approved or unapproved), except for the use of an approved drug in the practice of medicine, it involves the testing of the safety or efficacy of a medical device, or the data will be reported to or held for inspection by FDA.

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(6) **Good Clinical Practices (GCP):** The international ethical and scientific quality standard for designing, conducting, monitoring, recording, auditing, analyzing and reporting studies. Adhering to the GCP will ensure that the research data reported will be collected using credible and accurate methods to protect research participants' rights and confidentiality.

(7) **Health Insurance Portability and Accountability Act (HIPAA):** The regulation that includes under Title II an Administrative Simplification Compliance Act that applies to the following four areas: Patient privacy; Security of protected patient information; Standardization of transactions and code sets; and Standard Identifiers for such entities as employers and healthcare providers.

(8) **Human Biological Specimen:** A human biological specimen is any material(s) derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings, or any other cells, whether collected for research purposes or as a residual specimen from a diagnostic, therapeutic, or surgical procedure.

(9) **Human Research Protection Program (HRPP):** The systematic and comprehensive approach by an organization to ensure human subject protection in all research. The implementation of any part of the program may be delegated to specific committees, individuals or entities, by the organization.

(10) **Human subject:** The STVHCS oversees and conducts research that is covered by both the Department of Veterans Affairs and Department of Health and Human Services (to include FDA) regulations, therefore, the definition of human subject (also called a research participant) employed by the STVHCS HRPP includes both DHHS (and VA) and FDA definitions:

(a) Department of Health and Human Services (DHHS) and Department of Veterans Affairs (DVA) definitions: 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. Intervention includes both physical procedures by which data are gathered and manipulations of the subject or the subject's environment that are performed for research purposes. Interaction includes communication or interpersonal contact between investigator and subject.

(b) FDA definition: 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 human or a patient. Under 21 CFR 812 this also includes an individual on whose specimen an investigational device is used.

(11) **Human subject research:** Human subject research includes all research meeting the definition of "research" (see section 2.b.(23)) performed with "human subjects" (see section 2.b.(10)). VA also defines human subjects research to include research involving human biological specimens. A human specimen obtained from a commercial source with no identifying information, when used in research, does not constitute human subjects research.

(12) **Informed Consent:** Informed consent is a process, not just a form. It is a fundamental mechanism to ensure respect for persons through provision of thoughtful consent for a voluntary act. Information provided in the informed consent process must be presented in terms that the subject population can understand, to enable persons to voluntarily decide whether or not to participate as a research subject. The written presentation of information is used to document the basis for consent and for the subjects' future reference. The process of obtaining informed consent must comply with the requirements of 45 CFR 46.116 and the documentation of informed consent must comply with 45 CFR 46.117.

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(13) **Institutional Review Board (IRB):** An independent committee comprising scientific and non-scientific members established according to the requirements outlined in Title 38, part 16 (same as Title 45, part 46 and Title 21, part 56) of the U. S. Code of Federal Regulations. The IRB may also be referred to as the Human Studies Subcommittee of the Research & Development (R&D) Committee.

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

(15) **Investigational drug:** An investigational drug is a drug or biological drug that is used in a clinical investigation. The FDA considers the term "Investigational New Drug (IND)" synonymous with investigational drug (21 CFR 312.3). However, for purposes of this Policy Memorandum, an Investigational Drug may be an approved drug that is being studied for an unapproved or approved use in a controlled, randomized or blinded clinical trial.

(16) **Investigator:** An investigator, as defined by VHA Handbook 1200.5 is an individual under the direction of the Principal Investigator (PI) who is involved in some or all aspects of the research project, including the: design of the study, conduct of the study, analysis and interpretation of the collected data, and writing of resulting manuscripts. An investigator must be either compensated by VA, be appointed to work without compensation (WOC), or may be an employee assigned to VA through the Intergovernmental Personnel Act (IPA) of 1970.

(17) **Legally Authorized Representative.** A legally authorized representative is an individual or body authorized under applicable law to provide permission on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research.

(18) **Memorandum of Understanding (MOU):** A written agreement outlining the details of the relationship between organizations, including the responsibilities of each. Such an agreement is used by the STVHCS to delineate the terms and conditions under which the STVHCS utilizes the IRB of the affiliated University of Texas Health Science Center (also called the "affiliate").

(19) **Non-compliance:** Conducting research in a manner that disregards or violates federal regulations or institutional policies and procedures applicable to human research (including the requirements of the VA Handbook 1200.5 and other VA policies and regulations, as applicable) which can be characterized by severity of the event and the pattern of like or similar events. Noncompliance with IRB and/or federal requirements may involve a range of issues from relatively minor or technical violations which result from inadvertent errors, inattention to detail, or inadequate training and supervision of research staff to more serious noncompliance. **Serious noncompliance** is defined as noncompliance that adversely affects subject safety or the safety of others, increases the risks to subjects, and/or violates the rights and welfare of participants (any of which may also be an unanticipated problem). Serious noncompliance may affect the subject's willingness to participate in research or may affect the integrity of the data (which may also be scientific misconduct). **Continuing noncompliance** is a pattern of recurring (involving one or more protocols simultaneously or over a period of time) or ongoing instances of actions or omissions (noncompliance) which indicate an underlying deficiency in knowledge of the regulations and IRB requirements, or a possible inability or unwillingness to comply with them. Instances of continuing noncompliance may or may not constitute serious noncompliance.

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(20) **Office for Human Research Protections (OHRP):** The Federal government office that issues assurances and oversees compliance with regulations concerning human research.

(21) **Office of Research Oversight (ORO):** The Veterans Health Administration (VHA) office that will advise the Under Secretary for Health on matters related to the protection of human research subjects, animal welfare, research safety, and research misconduct. ORO supports and promotes the responsible conduct of research through periodic inspections and evaluations of research integrity, and through investigations of allegations of non-compliance with policies and regulations at VA research facilities.

(22) **Principal Investigator (PI):** Within VA, a PI is an individual who conducts a research investigation, i.e., under whose immediate direction research is conducted, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team. The FDA considers a PI and an investigator to be synonymous. The PI is accountable for the proposal and the execution of the research protocol, as designed, by overseeing the performance of research staff to ensure the completion of all research activities.

(23) **Protocol:** A plan that includes, at a minimum, the objectives, rationale, design, methods and other conditions for the conduct of a research study.

(24) **Research:** The STVHCS oversees and conducts research that is covered by both the Department of Veterans Affairs and Department of Health and Human Services (to include FDA) regulations, therefore, the definition of research employed by the STVHCS HRPP includes both DHHS (and VA) and FDA definitions:

(a) DHHS and DVA definitions: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of the STVHCS HRPP, even if they are conducted or supported under a program that is not typically considered research. For example, some demonstration and service programs may include research activities.

(b) FDA definition: Clinical investigation (Per FDA Title 21 CFR 50 & 56) means any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit.

(25) **Research Impropriety:** Research impropriety is any ethical lapse or other impropriety involving or occurring in connection with research other than research misconduct as defined in paragraph 4y. Examples of research impropriety include, but are not limited to, conflicts of interest, misallocation of funds, sexual harassment, discrimination, and breaches of human subjects protections and animal welfare requirements. Some instances of research impropriety may also meet the definition of research noncompliance.

(26) **Research misconduct:** Fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results.

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(27) **Serious Adverse Event (SAE):** Any Adverse Event that results in death, a life threatening situation, hospitalization or prolonged hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. SAEs require reporting to the sponsor and the IRB in accordance with IRB policy and procedure.

(28) **Sponsor:** Any person or entity that takes responsibility for and initiates a clinical study. The sponsor may be an individual, pharmaceutical company, device manufacturer, governmental agency, academic institution, private organization, or other organization.

(29) **Test article:** any drug for human use, biological product for human use, medical device for human use, or other article used in a clinical investigation involving human subjects or their specimens.

(30) **Unanticipated Problems Involving Risk to Subjects and Others (UPIRSO):** Any event or information that (1) was unanticipated and (2) at least possibly related and (3) involves greater risk to subjects or others.

(a) Unanticipated: Not consistent with either the described risks in the research documents, or not expected as part of natural progression of subjects underlying condition (increases in frequency or severity are considered to be unanticipated).

(b) At Least Possibly Related: Intervention or interaction in the research and/or related to collection of identifiable private information in the research considered more than likely than not (e.g. >50% chance), that it is at least partially related.

(c) Greater Risk of Harm: Suggests that the research places subjects or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

(31) **VA Research:** All research, and all other activities that in part involve research, is considered VA research and is subject to evaluation and approval by the VA R&D Committee and other VA regulation, if any of the following conditions are met:

(a) The research is sponsored by the VA.

(b) The research is conducted by or under the direction of any salaried or without compensation (WOC) employee of the STVHCS during and in connection with her/his STVHCS responsibilities.

(c) The research is conducted using any property or facility of STVHCS.

(d) The research recruits subjects at the STVHCS or uses the STVHCS's nonpublic information to identify or contact human research subjects for research purposes.

(e) The funds for the research activities are managed by the STVHCS or its affiliated non-profit corporation, the Biomedical Research Foundation of South Texas.

### **3. ACTION:**

**a. MISSION OF THE STVHCS HRPP:** The STVHCS is committed to accomplishing the following mission:

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(1) To advance the protection and well being of research subjects by creating a dynamic and collegial environment of respect and understanding of the rights and welfare of human research participants.

(2) To foster high ethical standards for the conduct of research involving humans.

(3) To ensure Investigators use sound scientific design in conduct of research.

(4) To continually provide research administrative staff, investigators and their research staff with the current up-to-date information on regulations and ethical principles regarding human protection and research.

(5) To continually assess the effectiveness of the multiple components of the HRPP, including the IRB and the R&D Committee, in their protection of human subjects, review of research, and compliance with federal regulations.

(6) To continually review and implement new approaches to advance the responsible conduct of research and protection of human research subjects.

### **b. PRINCIPLES GOVERNING THE HRPP:**

(1) **Ethical principles:** All activities related to human subject research at the STVHCS, regardless of funding source, will be guided by the ethical principles found in the *Ethical Principles and Guidelines for the Protections of Human Subjects of Research* (the “Belmont Report”) and governed by the Federal policy for the Protection of Human Subjects (Common Rule) codified by the VA at 38 CFR 16 and VHA Handbook 1200.5. The ethical principles defined in the Belmont Report are as follows:

(a) **Beneficence** – The sum of the benefits to the subject and the importance of the knowledge to be gained outweigh the risks to the subjects as to warrant a decision to allow the subject to accept these risks.

(b) **Autonomy** – Legally effective informed consent is obtained, unless the requirements for waiver of informed consent are met by adequate and appropriate methods in accordance with the provisions of applicable regulations.

(c) **Justice** – The selection of subjects is equitable and is representative of the group that will benefit from the research.

Because exempt research does not fall under the normal regulatory requirements, review of this research by the R&D Committee, and Privacy Office will include a review to identify any ethical issues that would preclude the conduct of the research at the STVHCS.

(2) **Integration and Cooperation:** In order to fulfill its human research protection obligations, the STVHCS distributes responsibilities to various interdependent entities and individuals, each with its own set of responsibilities, creating an integrated system for protecting human research subjects. The ethical conduct of research is a shared responsibility, requiring cooperation, collaboration, trust, and effective communication. The HRPP includes institutional officials, the Research and Development (R&D) Committee and its subcommittees, the Institutional Review Boards (IRB), R&D staff, Compliance Office, Research Pharmacy, investigators and staffs, and various other elements and individuals.

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(3) **Continuous improvement:** The STVHCS HRPP is a flexible and dynamic program, continually being changed and refined to effectively meet the goals of providing human research protection. All components of the HRPP have the responsibility and capacity to effect change to better provide protection in human subjects research.

### c. AUTHORITY FOR THE HRPP

(1) **Assurances:** The STVHCS has given and maintains written assurance in a Federal-Wide Assurance (FWA) with the Office of Human Research Protections (OHRP) that it will comply with the Department of Health and Human Services regulations for the protection of human research subjects, 45 CFR Part 46, as amended, to include provisions of the Federal Policy for the Protection of Human Subjects. This assurance states that the institution is guided by the ethical principles regarding all research involving human subjects, as set forth in the report of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research entitled Ethical Principles and Guidelines for the Protection of Human Subjects of Research (The “Belmont Report”). The Assurance sets out the responsibilities for protecting human subjects. The STVHCS operates under Federal Wide Assurance #FWA00001220. The signatory official for the FWA is the Director of the STVHCS.

(2) **Federal regulatory guidelines:** In addition to the FWA, authority and direction for the HRPP comes from a large body of VA and other federal regulations. These are listed as references at the end of this policy.

(3) **State laws and regulations:** Texas State law differs slightly from VA regulations pertaining to the definition of Legally Authorized Representative. As a general rule, the STVHCS follows the more restrictive of the regulations.

(a) In the State of Texas a legally authorized representative of a subject who provides consent for a patient with impaired decision-making capacity (surrogate consent) is a health care agent appointed by the person in a Durable Power of Attorney for Health Care (DPAHC); court-appointed guardian of the person, or from next-of-kin in the following order of priority: the patient’s spouse, an adult child of the patient who has the waiver and consent of all other qualified adult children of the patient to act as the sole decision-maker; a majority of the patient’s reasonably available adult children, patient’s parents, the individual clearly identified to act for the patient by the patient before the patient became incapacitated, the patients’ nearest living relative, or a member of the clergy.

(b) Texas state law defines an “adult” as someone 18 years of age or older OR someone less than 18 years of age but who has had the disabilities of minority removed by court order, unless the court ordered a limited removal that does not include health care decision-making capacity.

(c) Texas state law also provides additional regulations related to the surrogate consent for foster children.

(d) Where there is a question of interpretation of applicability State law, the Regional Counsel for the STVHCS is consulted.

(4) **Local Policies and Procedures:** The diverse activities of the HRPP are outlined in various local policies and procedures. These include, but are not limited to, policy memorandums and standard operating procedures from the involved components, such as the R&D office (e.g. training, QA

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Subcommittee, processing complaints, WOC appointments), Pharmacy Service (Investigational Drugs), Compliance Office (Quality Assurance/Quality Improvement).

(5) **Legal counsel:** Where there is a question of applicability of federal and other regulations and guidance, the Regional Counsel for the STVHCS is consulted.

### **d. CONDITIONS UNDER WHICH HUMAN RESEARCH BECOMES SUBJECT TO THE STVHCS HRPP**

(1) **Human Research Subjects and the STVHCS HRPP:** When research involving human subjects meets the definition of “VA Research” (paragraph 4.dd), this research is subject to the STVHCS HRPP. The research may be VA funded, funded from extra-VA sources, or conducted without direct funding. Any questions concerning whether an activity is human subject research at the STVHCS should be brought to the IRB director, ACOS for R&D, or R&D Committee Chair.

(2) **"Engaged" In Human Subjects Research:** The STVHCS is considered "engaged" in human subjects research under our FWA and the research is subject to our HRPP when STVHCS employees or agents (all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility either through salaried or without compensation [WOC] appointments) are involved in the following:

(a) Intervening with living individuals by performing invasive or noninvasive procedures for research purposes (e.g., drawing blood; collecting other biological samples; dispensing drugs; administering other treatments; employing medical technologies; utilizing physical sensors; utilizing other measurement procedures);

(b) Manipulating the environment for research purposes (e.g., controlling environmental light, sound, or temperature; presenting sensory stimuli; orchestrating environmental events or social interactions);

(c) Interacting with living individuals for research purposes (e.g., engaging in protocol-dictated communication or interpersonal contact; conducting research interviews; obtaining informed consent);

(d) Releasing individually identifiable private information, or permitting investigators to obtain individually identifiable private information, without subjects' explicit written permission (e.g., releasing patient names to investigators for solicitation as research subjects; permitting investigators to record private information from medical records in individually identifiable form);

(e) Obtaining, receiving, or possessing private information that is individually identifiable (either directly or indirectly through coding systems) for research purposes, including maintaining "statistical centers" for multi-site collaborative research.

**e. RESEARCH CONDUCTED AT THE STVHCS:** Research conducted at the STVHCS has the overall goal to advance health care for our veteran population and the nation. The STVHCS HRPP covers all types of human subjects research conducted at the STVHCS, including:

(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.

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(2) **Social and Behavioral Research.** 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.

(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).

(4) **Health Services and Epidemiology Research.** Health Services and 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. Data may be collected through surveillance, monitoring, and reporting programs or may employ retrospective review of medical, public health, and/or other records or databases. Because this type of research often involves aggregate examination of data, it may not always be necessary for the investigator to collect individually identifiable information. When this is the case, the research may qualify for exemption or expedited review. In all cases, the IRB Director or his/her designated reviewer, not the individual investigator, will determine when IRB review of the activity is required.

(5) **Research Involving a Data Repository or Tissue Bank:** Research utilizing stored data and/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 and R&D Committee 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. VA-sponsored tissue banks must follow VHA Directive 2000-043 "Banking of Human Research Subject's Specimens".

(6) **Activities that may or may not be research:** Several activities may or may not constitute research, depending on whether the activity is designed or intended, at least in part, to develop or contribute to generalizable knowledge. A tool for determining when an activity is considered research is found in the Attachment. Investigators should seek input from the IRB Director and/or ACOS for R&D if they have questions on when an activity constitutes research.

(a) **Quality Improvement Activities:** Quality Improvement activities attempt to measure the effectiveness of programs or services and often provide recommendations for improvement. Quality Improvement activities constitute human subject research, and require IRB review, when they involve human subjects and are designed or intended, at least in part, to develop or contribute to generalizable knowledge. On the other hand, Quality Improvement 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. In cases where the intent of the activity changes after it has begun (e.g., findings from an activity intended solely for internal STVHCS purposes lead to a desire to generalize and disseminate the results for application outside the STVHCS), the activity becomes research at the moment the intent to generalize the findings is formed, and the IRB should be contacted immediately. In all cases, it is the IRB, not the investigator, which will determine when an activity constitutes research and the conditions under which the investigator may pursue the research objectives.

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(b) **Innovative Treatments in Medical Practice:** In the course of medical practice, clinical judgment sometimes leads physicians to employ “innovative” or “off-label” treatments when more common treatments appear to be ineffective or otherwise unsuitable in addressing a patient’s 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. In all cases, it is the IRB, not the investigator, which will determine when an activity constitutes research and the conditions under which the investigator may pursue the research objectives.

(c) **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. A retrospective review of a series of cases with the intent of publishing a generalizable conclusion would be considered research and requires approval by the IRB and R&D Committee.

### **f. RESEARCH NOT CONDUCTED, OR CONDUCTED UNDER SPECIAL RESTRICTIONS, AT THE STVHCS:**

(1) Research in which the subject is a fetus, in-utero or ex-utero (including human fetal tissue) will not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

(2) Research related to in vitro fertilization will not be conducted by STVHCS investigators while on official duty, or at VA facilities, or at approved off-site facilities.

(3) Research involving prisoners as participants will not be conducted at the STVHCS unless the additional criteria in the VA Handbook 1200.5 Appendix D are met.

(4) Research involving children will not be conducted by STVHCS investigators while on official duty or at VA or approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer.

(5) Research involving pregnant women as participants will not be conducted at the STVHCS unless the additional criteria in the VA Handbook 1200.5 Appendix D are met.

(6) Research involving subjects who are mentally ill or subjects with impaired decision-making capacity will not be conducted at the STVHCS unless the additional VA criteria in the VA Handbook 1200.5 Appendix D are met.

(7) Research involving the conduct of planned emergency research without informed consent, per 21CFR 50.54, will not be conducted by VA investigators while on official duty, or at VA facilities, or at approved off-site facilities.

### **g. SUBJECTS THAT PARTICIPATE IN RESEARCH AT THE STVHCS**

(1) **Veterans:** Research subjects that participate in studies at the STVHCS are typically veterans receiving health care from the STVHCS.

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(a) Adults with independent decision-making capacity, which may include healthy volunteers and those with conditions that affect the veteran population.

(b) Adults who are incompetent or have impaired capacity for decision-making may also be included as long as the procedures and conditions detailed in VHA Handbook 1200.5 (paragraph 11; and Appendix D, paragraph 6), designed to protect these subjects from exploitation and harm, are met.

(2) **STVHCS staff:** The professional and support staff of the STVHCS may be included in a research study. Special permissions must be obtained for staff to participate during their work hours, and care must be taken to ensure that participation in a study is voluntary and does not influence their employment performance or standing.

(3) **Non-veterans:** Non-veterans may be entered into VA approved research studies only when there are insufficient veterans available to complete the study and in accordance with 38 CFR 17.45 and 38 CFR 17.92. All regulations pertaining to the use of veterans as research subjects pertain to non-veteran subjects enrolled in VA approved research.

### **h. ORGANIZATIONAL STRUCTURE AND RESPONSIBILITIES OF THE HRPP—**

The essential functions of the STVHCS HRPP include comprehensive review of protocols, ethically sound participant-investigator interactions, ongoing (risk appropriate) safety monitoring, quality improvement / compliance activities, and education and training of investigators and research staff. It is the responsibility of all individuals involved in the HRPP to understand and apply their obligation to protect human subjects.

#### **(1) Medical Center Director:**

(a) The Director is the institutional official ultimately responsible for the implementation and performance of the STVHCS HRPP. The Director is advised and assisted by the R&D Committee.

(b) The Director is the Assurance signatory official and is responsible for overseeing the protection of human subjects within the facility.

(c) The Director ensures that policies and procedures for the HRPP are developed and maintained. The Director is responsible to see that sufficient resources, including funding, space and staff to support the activities of the HRPP are provided.

(d) The Director ensures that an environment that fosters safe human subjects research is promoted and training and education for all participants in the HRPP is provided.

(e) The Director is ultimately responsible for overseeing the IRB in its review and monitoring of VA human subject research, and assuring that IRB members are appropriately knowledgeable in the protection of human subjects and understand their ethical obligation to do so.

(f) The Director is ultimately responsible for the oversight of VA investigators and assuring that investigators are appropriately knowledgeable and understand their obligation to conduct research in accordance with ethical standards and all applicable regulations.

(2) **R&D Committee:** The R&D Committee has a central role in the oversight of research at the STVHCS. The responsibilities and function of the R&D Committee are detailed in STVHCS Policy

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Memorandum 151-08-02. In broad terms, the R&D Committee is responsible through the Chief of Staff to the facility Director for the following:

(a) Maintaining high standards throughout the R&D program, including the protection of human research subjects.

(b) Ensuring the scientific quality, sound design, safety, and appropriateness of all research involving human subjects relative to the Belmont Report and VA and other Federal regulations. The research should have the ability to answer the proposed questions and contribute to knowledge of the field.

(c) Ensuring that the resources available for the proposed research are adequate to successfully and safely perform the research.

(d) Overseeing the implementation and performance of the HRPP and provides the overall oversight to assure regulatory compliance. It has the responsibility to assure that there is adequate resource allocation to maintain the HRPP.

(e) Reviewing all subcommittee activities, and ensures that the procedures followed for the review of research by the subcommittee are appropriate and free from undue influence.

(f) Evaluating quality improvement activities, supporting implementation of needed changes, and making recommendations to the Medical Center Director.

(g) Approving all research to be conducted within the STVHCS. No STVHCS research can be initiated without the approval of the R&D Committee.

(h) Exercising the ultimate authority to determine if a protocol involves human subject research. If a protocol is defined as not involving human subjects, the R&D Committee must assure that that definition is correct.

### **(3) Subcommittee for Human Studies (Institutional Review Board; IRB):**

(a) The STVHCS Director, as authorized by VHA Handbook 1200.5, has designated the UTHSCSA Institutional Review Board (IRB) as the Subcommittee for Human Studies that will review all human subject research at the STVHCS. The STVHCS has established a Memorandum of Understanding (MOU) with the UTHSCSA outlining the responsibilities and conditions of this arrangement. The STVHCS does not allow the use of a commercial IRB for VA research.

(b) The UTHSCSA IRBs are registered with OHRP: IRB 1, Full Reviews (Registration #IRB00000553); IRB 2, Continuing Reviews (Registration #IIRB00002691); and IRB 3, Full Reviews (Registration #IRB00002692).

(c) The IRB is responsible to review and monitor research involving humans subjects in accordance with Veterans Health Administration (VHA) guidelines, and will function as a subcommittee of the R&D Committee. The IRB has the authority to approve, require modifications necessary for approval, and disapprove all research activities involving human subjects at the STVHCS. No VA research involving human subjects may be initiated without approval of the IRB. The IRB will confirm that the research has a valid IND or IDE as appropriate.

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(d) The IRB has the authority to suspend or terminate the approval of research that is not being conducted in accordance with the IRB's requirements, or that has been associated with unexpected serious harm to subjects.

(e) The IRB has the authority to observe, or have a third party observe, the consent process and the conduct of human subject research.

(f) The UTHSCSA IRBs provide the relevant documents (e.g. protocols, copies of the minutes and IRB actions) to the R&D Committee to enable it to oversee the IRB review process. The R&D Committee may not approve research projects disapproved by an IRB.

(g) The IRB Director, not the investigator, makes the determination of when a protocol is exempt from federal regulations based on criteria detailed in 45CFR46.101(b)(1)-(6) and in accordance with VHA Handbook 1200.5. The IRB Director may delegate this authority to a designated reviewer. For VA research the R&D Committee will review the exempt determination by the IRB and has the authority to disapprove the research at the STVHCS if it does not agree with the IRB's exempt determination. In such cases, the R&D Committee will inform the IRB (and PI) in writing of its determination.

(h) The IRB is responsible for the dissemination of its policies, SOPs, and other materials necessary for the protection of human subjects.

### **(4) Quality Assurance/Quality Improvement (QA/QI) Subcommittee:**

(a) The R&D Committee has delegated its responsibility to review audit reports and QA/QI activities to its QA/QI Subcommittee.

(b) The QA/QI Subcommittee is tasked with developing plans and processes for improvement of research oversight, and evaluating research audit reports, reports of UPIRSOs, research non-compliance, and research-related concerns or complaints. Audit reports may include audits conducted by the STVHCS Compliance Office, Office of R&D, other STVHCS sections, or non-STVHCS audits such as by the UTHSCSA Compliance Office or external study monitors.

(c) The QA/QI Subcommittee forwards to the R&D Committee any recommendations for changes/corrective actions.

### **(5) ACOS for R&D and R&D Office:**

#### **(a) ACOS for R&D and Assistant Chief for Clinical Research:**

1 The responsibility to administer the R&D program and ensuring day-to-day operation (implementation, maintenance, and improvement) of the HRPP is delegated to the ACOS for R&D from the Medical Center Director through the Chief of Staff. This includes the financial management of the facility's HRPP program, funds allocated to each project, and any non-VA monies available in the Facility's General Post Fund designated for R&D activities by the Medical Center Director.

2 The ACOS for R&D serves as a member of the R&D Committee, reporting on the status of all aspects of research.

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3 The ACOS/R&D is the primary point of contact for communication between the IRB and the UTHSCSA Office of Clinical Research and the STVHCS HRPP.

4 The Assistant Chief for Clinical Research assists the ACOS for R&D in all aspects of the operational management of the STVHCS clinical research program and HRPP.

5 Any recommendations approved by the R&D Committee are implemented by the Associate Chief of Staff (ACOS) for R&D or his/her designee.

6 The ACOS for R&D ensures that all research personnel have designated roles and responsibilities delegated by the Principal Investigator that are appropriate to their education, training, licensure and experience, by reviewing and approving (along with the Chief of Staff) a written Research Scope of Practice.

**(b) The Administrative Officer (AO) for R&D and the R&D Office** administers the operational function of the HRPP. The AO for R&D is responsible for developing and implementing control procedures for fiscal matters, supplies, equipment, and services such as common resources and administrative support. The R&D Office responsibilities include:

1 Administration of the R&D Committee and its subcommittees.

2 Administration of the protocol review, management, and monitoring processes.

3 Processing research complaints or reports of noncompliance.

4 Verification, documentation, and tracking of required human research training and credentialing of research study personnel.

5 Preparation, submission, and maintenance of communications, reports, and correspondence required for the program administration.

6 Development, dissemination and implementation of VA Central Office policies and directives, and local policies and procedures. This requires the continual monitoring of VA and external guidance that affects HRPP activities and developing/implementing new or revised policies/procedures as required. Dissemination of information, and the provision of individualized consultation, related to new regulations, policies, and guidelines to research investigators, research staff, the R&D Committee, and the UTHSCSA Office of IRB are of critical importance to the function of the HRPP.

7 Providing an annual HRPP report to the R&D Committee to include a review of HRPP activities, changes in the HRPP, policies, budget and resources, training/credentialing, and Strategic Improvement and Quality Assurance/Quality Improvement activities.

### **(6) Investigational (Research) Pharmacy:**

(a) The Research Pharmacy, which is a part of the STVHCS Pharmacy Service, is responsible for implementation and monitoring of HRPP requirements associated with the use of investigational drugs and devices. The policies and procedures related to the handling of Investigational Drugs and Investigational Devices are detailed in STVHCS Policy Memorandum 119-08-05 and 119-08-21, respectively.

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(b) The research pharmacy is involved in all phases of investigational drug studies, from planning through completion.

(c) The Research pharmacist is an ex officio, non-voting member of the R&D Committee. For all submitted research protocols that include administration of test agents or devices, the Research Pharmacist provides for the R&D Committee a review of the safety, feasibility, and appropriateness of the study for the STVHCS, and ensures that pharmacy resources are adequate to support the research study.

(d) The responsibilities of the Research Pharmacy and Research Pharmacist related to the HRPP are many, and are detailed in STVHCS Policy Memorandum 119-08-05 and 119-08-21.

**(7) Compliance Office:** The Compliance Office has been delegated the following responsibilities by the Medical Center Director:

(a) Evaluating, through systematic audits, the institution's adherence to applicable federal and state regulations and accreditation standards governing human subject research.

(b) Evaluating, through systematic audits, the functions of the affiliated UTHSCSA IRB as they relate to VA policies.

(c) Evaluating the investigator's compliance of human research protections and adherence to applicable regulations and procedures.

(d) Evaluating the compliance of the Research Pharmacy to federal, VHA, and local regulations and policies.

(e) Evaluating the institution's quality improvement and quality assurance programs to establish systematic monitoring procedures for the human subject research programs.

(f) Communicating its audit findings through written reports to the VA R&D Committee (through the Quality Assurance/Quality Improvement Subcommittee), the UTHSCSA IRB, and the UTHSCSA Compliance Office when the study is also active at the UTHSCSA. An audit review plan is maintained that includes measuring, assessing, and reporting findings on an ongoing basis. Findings that require prompt action by the IRB and/or R&D Committee will be reported directly to the Chair of the committee.

**(8) Principal Investigators (PI's) and their research staff:** All individuals involved in research at the STVHCS must have either a salaried or Without Compensation (WOC) appointment. Principle Investigators have the primary responsibility to safeguard the rights and welfare of each research subject, and to ensure that the subject's rights and welfare take precedence over the goals and requirements of society and the research. Any questions related to this responsibility, or the policies and procedures for protection of human subjects, should be directed to the IRB Director or ACOS for R&D. The Principal Investigator and research staff must abide by all determinations of the IRB and R&D Committee. The responsibilities of the Principal Investigator include but are not limited to:

(a) Ensuring that the research protocol has sound design, minimizing risks to subject while maximizing research benefits. Non-research procedures and data should be used to avoid adding risk or inconvenience to the subject when possible.

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(b) Conducting the study in such a way as to protect the rights and welfare of human subjects, in accordance with the principles, standards, and requirements set forth in the *Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research*, U.S. Department of Health and Human Services regulations, and any other relevant National, State, or Institutional laws or regulations.

(c) Conducting the study and enrolling subjects in accordance with the IRB and R&D approved current protocol and making changes to the protocol only with approval of the sponsor (if any), Institutional Review Board (IRB), and R&D Committee, except in emergent situations when the changes are necessary to protect the safety, rights or welfare of subjects.

(d) Ensuring that research subjects are fully informed of the investigational purpose of the study and the potential risks, and that all requirements relating to the adequacy of both the informed consent document and the informed consent process, including its documentation, are met.

(e) Exercising effective oversight of all activities related to the protocol and ensuring that all research personnel involved in the conduct of the study are informed about their responsibilities, have been appropriately trained, and work within their approved Scope of Practice.

(f) Ensuring appropriate data safety and monitoring for the protocol, monitoring of subjects for potential harm, promptly modifying of the research design to mitigate any potential risks, and reporting any changes in the risk-benefit ratio to the IRB.

(g) Ensuring that resources are adequate to effectively and safely perform the research as described in the protocol.

(h) Reporting to the sponsor and the IRB any unanticipated problems involving risk to subjects or others (UPIRSO) and research noncompliance that occur in the course of the research in compliance with applicable policies.

(i) Maintaining appropriate documentation (enrollment, research progress, and termination notes) in the subject's electronic medical record.

(j) Maintaining adequate and accurate source documentation and regulatory records in accordance with the Sponsor's regulations and GCP. Records must be properly secured and available for inspection in accordance with applicable National and Institutional regulations.

(k) Ensuring that VHA and STVHCS pharmacy regulations are followed if the study involves any test article, including that a drug or device has an IND or IDE or meets criteria for exemption. Conducting research involving FDA-regulated products in compliance with all applicable FDA regulations, and fulfilling all FDA-directed investigator (or Investigator-Sponsor) responsibilities (including maintaining an accurate FDA 1572 form when appropriate).

(l) Ensuring that the privacy and personal information of research subjects and research data is protected and disclosures are accounted for according to VA, Federal, State, and Institutional regulations.

(m) Ensuring timely submission of information to the IRB, R&D Committee, and Compliance Office so that effective oversight of the research is maintained.

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(n) Providing the R&D Office with all STVHCS Report of Clinical Research Monitoring Visit forms from all external study monitoring visits.

(o) Disclosing any financial Conflict of Interest relevant to the study to the STVHCS Financial Conflict of Interest Administrator and the IRB.

(p) Ensuring that recruitment of subjects is performed in a fair and equitable manner and in accordance with all IRB, STVHCS, VHA, and other federal regulations.

(q) Reporting any concerns, complaints, allegations of research improprieties, or research misconduct to the R&D office, who will assure communication to the appropriate component of the HRPP.

(r) Responding to participants' questions, concerns, and complaints in an efficient and appropriate manner.

**(9) Information Security Officer (ISO):** The ISO works closely with the R&D Office, and the R&D Committee to ensure that all research data is collected, handled, and stored in a secure manner. The ISO reviews each research protocol that is submitted to the R&D Committee, and no protocol will be approved that does not meet the VA research data security standards as described in Research Service Standard Operating Procedure 08-35. The ISO is an ex officio, non-voting member of the R&D Committee and is responsible to communicate to the R&D Committee on any matter of concern related to information security in research.

**(10) Privacy Officer:** The Privacy Officer is responsible to review all IRB-approved studies to ensure that legal authority exists prior to the use of Protected Health Information (PHI) for research, and that legal authority exists prior to the disclosure of PHI to outside entities for research purposes. The Privacy Officer participates as an ex officio, non-voting member of the R&D Committee in order to review research documentation and raise privacy issues directly to the R&D Committee. The Privacy Officer is responsible to monitor the accounting of disclosures of PHI related to research.

**(11) Medical Staff Office:** The Medical Staff Office has the responsibility of verifying the appropriate credentials of the Licensed Independent Practitioners involved in research, and for providing current information to the R&D Office for verification and tracking of credentials for research investigators.

**(12) Human Resources Management Service (HRMS):** The HRMS has the responsibility of processing and maintaining appointments of all personnel involved in STVHCS research.

**(13) Financial Conflict of Interest (FCOI) Administrator:** The FCOI Administrator is appointed by the Medical Center Director to review research investigator's FCOI disclosure forms to determine if a real or perceived FCOI may exist. The Administrator will consider the FCOI evaluation by the IRB in determining the actions required to manage, reduce, or eliminate FCOI, and will make referrals to Regional Counsel when necessary. The findings and recommendations of the FCOI Administrator will be communicated to the IRB and R&D Committee. No protocol will be approved by the R&D Committee unless all of the concerns of the FCOI Administrator and the IRB FCOI evaluation are satisfied.

**(14) Radiation Safety Committee (Medical Radioisotope and Radiation Control Committee; MRRCC):** The IRB and R&D Committee cannot approve research involving the use of

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radioactive substances or radiation at the STVHCS unless it has been approved by the MRRCC. The MRRCC is responsible to:

(a) Review and approve or deny, on the basis of scientific validity, safety, feasibility, and appropriateness for the STVHCS, any research protocol that involves the use of radioactive materials and radiation producing devices.

(b) Review and approve or deny a proposed authorized user, based on the training and experience of the individual, to ensure that the qualifications of all investigators involved in protocols that use radioactive materials are adequate.

(c) Review investigation reports of all alleged occupational overexposures, recorded events, misadministration and unusual occurrences as they pertain to the use of radioactive materials and radiation devices.

(d) Recommend actions indicated to reduce or minimize radiation exposure, and direct termination of those activities, involving radiation or radioisotopes, that seriously threaten the health of any individual.

(e) Ensure the safety review of the use of potentially hazardous sources of non-ionizing radiation for the STVHCS.

**(15) Subcommittee for Research Safety (SRS):** The SRS is a subcommittee of the R&D Committee that is responsible for overseeing compliance with the VHA Handbook 1200.8 Safety of Personnel Engaged In Research. The details of the STVHCS Research safety program and function of the SRS can be found in the SRS Policy. The responsibilities of the SRS include the following:

**(a) Reviewing research proposals for compliance with all applicable regulations pertaining to biological, chemical, physical, and radiation hazards. This includes all research proposals to be conducted at the VA, or by VA personnel off-site while on-duty.** The SRS will approve or disapprove all proposals that involve safety hazards unique to the research environment, and will provide written communication of the committee's findings to the PI and the R&D Committee. The R&D Committee will consider the findings of the SRS prior to its approval of the research protocol.

**(b) Making general recommendations to the R&D Committee, ACOS/R&D, Chief of Staff, facility safety official, and when appropriate, facility safety committee regarding research safety.**

(c) Identifying the need for health surveillance of personnel involved in individual research projects; and if appropriate, advising R&D Committee and Employee Health Practitioner on the need for such surveillance.

(d) Communicating with, and serving as an information resource to, investigators and research staff concerning all aspects of research safety.

(e) Reporting annually to the R&D Committee an evaluation of the STVHCS research safety program, to include a review of all active research protocols involving biological, chemical, physical, and radiation hazards, regardless of funding status or source, an assessment of the effectiveness of the research safety program, and recommendations for quality improvement.

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**(16) Medical Records Office:** The Medical Records Office is responsible to assist in the documentation of research activities in the medical record. The Medical Records office is responsible to scan and enter (attached to the Consent Enrollment Note) the signed Research Informed Consent Document (VA 10-1086 form), and the Investigational Drug record document (VA 10-9012 form) into the electronic medical record.

**(17) Research Integrity Officer (RIO):** The ACOS for R&D is designated by the STVHCS Director as the institution's RIO. He/she is responsible to receive, and ensure the appropriate investigation of any allegations of misconduct according to STVHCS Policy Memorandum 151-07-06) and VHA Handbook 1058.2.

**(18) Clinical Staff:** The STVHCS clinical staff (nurses, physicians, respiratory therapists, etc.) has the responsibility of contributing to the protection of human subjects when they interact with research subjects and investigators as part of their routine clinical duties. This includes communication with research staff, compliance office, or R&D Office staff when they have a question or concern about a research activity. The clinical staff is responsible to read the documentation of research activities in the medical record and use the information as appropriate in the routine clinical care of the patient.

**(19) UTHSCSA Office of Clinical Research:** The STVHCS research program is closely aligned with the research program at the UTHSCSA because investigators and research staff are dually salaried by the two institutions and may be principally located at either institution, research protocols are often active at both sites, and parts of VA-approved research may be performed at the UTHSCSA. The UTHSCSA Office of Clinical Research is the counterpart of the R&D Office at the STVHCS. These offices recognize that the optimal protection of human subjects requires full cooperation between the two institutions. Therefore, the offices work together in efforts such as jointly providing training for research personnel, using a shared evaluation tool for defining research Scope of Practice, sharing of research resources, and jointly implementing compliance activities.

**(20) External sponsors:** External sponsors of human subject research have a role in the protection of research subjects during all phases of the research.

(a) Prior to initiation of a sponsored research protocol, the written agreement between the organization and sponsor must specify that the sponsor will use procedures that protect research participants; address medical care for research participants with a research-related injury; promptly report to the Organization findings that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's approval to continue the study; address plans for disseminating findings from the research and the roles that investigators and sponsors will play in publication or disclosure of results; and address in the written agreement with the Sponsor how results will be communicated to study participants.

(b) During the active phase of the research the sponsor must promptly report to the Principal Investigator any finding that could affect the safety of participants or their willingness to continue participation, influence the conduct of the study, or alter the IRB's or R&D Committee's approval to continue the study. The PI must ensure that the IRB and STVHCS R&D Office are notified, as appropriate.

### **i. PROTECTION OF CONFIDENTIAL INFORMATION ABOUT RESEARCH SUBJECTS**

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(1) **Electronic data:** VA-sensitive research data (containing individually identifiable information) in electronic form must be stored, maintained, or utilized within the VA protected environment (behind the VA firewall), unless approval from the ACOS for Research and Development, Information Security Officer, Privacy Officer, and Hospital Director has been obtained.

(2) **Non-electronic data:** The storage of non-electronic data (paper copies and research specimens) must meet VHA physical security standards.

(3) **Access to the identifiable data:** Access to the identifiable data collected during research is limited to authorized individuals who are designated on the VA approved protocol.

(4) **Loss or compromise of VA-sensitive research data:** Any loss or compromise of the VA-sensitive research data must be reported promptly to the employee's supervisor, ACOS for R&D, and Information Security Officer at the STVHCS. If the data loss included individually identifiable information it should also be reported to the STVHCS Privacy Officer, and to the IRB as a UPIRSO.

(5) **Change in location of research data:** any transmission, transport, or use of the VA-sensitive data outside the approved location must be approved by the ACOS for R&D, Information Security Officer, and Privacy Officer of the STVHCS.

### j. INTERACTION AND COMMUNICATION BETWEEN THE COMPONENTS OF THE HRPP

(1) **Independence of review and oversight:** The STVHCS HRPP functions as a coordinated system of checks and balances provided by the multiple different review components (IRB, R&D, Privacy, Compliance). Each of the components functions independently in its review and oversight of research, and one component cannot exert undue influence on the independent review and conclusions of another. The R&D Committee and IRB do not answer to individuals, departments, or units that rely on them for the review of their research. The PI is responsible to assure that no undue influence will be asserted by any member of the research team toward any review or oversight committee, committee member, or individual involved in the HRPP. The R&D Committee is the final authority of all decisions regarding the welfare and protection of human subjects participating in research at the STVHCS, however, it cannot approve any research activity that has not been approved by the IRB. Likewise, Institutional Officials do not have the authority to approve research that has not been approved by the IRB and R&D Committee. The R&D Committee is responsible to ensure that the review process for each component is appropriate, without exerting undue influence on the outcome of a review of a specific protocol or activity. Attempts to exert undue influence on the review or approval process should be reported to the IRB Director, ACOS for R&D, or Medical Center Director.

(2) **Coordinated effort and effective communication:** The effective function of the multi-component and multi-tiered HRPP requires coordination at all levels and frequent and effective communication at all levels. The lines of communication and coordination are described in multiple Standard Operating Procedures and Policies.

(3) **Dissemination of Information:** All policies and SOPs related to the HRPP will be made available to investigators and research staff through electronic dissemination, posting on the STVHCS Research Service website, and through paper copy in the R&D Office.

### k. RESOURCES COMMITTED TO THE HRPP

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(1) The STVHCS will provide the resources appropriate to the volume of research at the STVHCS to ensure the effective function of the HRPP. It will engage in a systematic budgeting process for the HRPP resources including personnel, materials, space, equipment, training and education. Funding for the various components of the HRPP may come from the medical care allocation, R&D Service administrative funds, and the mandated (VHA Directive 2003-031) charge to industry-sponsored studies to defray the cost of HRPP activities.

(2) The R&D Office will report annually to the R&D Committee a review of resources provided by organization to support the HRPP. The R&D Committee will evaluate the effective function, quality, and compliance of the program, and will communicate its findings and any recommendations to the Medical Center Director.

**1. STRATEGIC IMPROVEMENT AND QUALITY ASSURANCE/QUALITY IMPROVEMENT RELATED TO THE HRPP:** The STVHCS program for the protection of human subjects is accomplished through a system of continuous education, evaluation, implementation, and oversight activities.

(1) **Education of research personnel:** The STVHCS recognizes that a proactive program of education for all individuals involved in human subjects research is critical to the success of the HRPP. To this end several educational programs and activities have been implemented.

(a) **On-line standardized training:** All individuals involved in human subjects research at the STVHCS, whether they are salaried or have a Without Compensation appointment, are required to annually complete the online CITI Course in The Protection of Human Research Subjects. A link to this training course is available on the STVHCS Research Service website.

(b) **Monthly research training seminars:** The STVHCS R&D Office provides monthly seminars for investigators and their research staff related to the responsible conduct of human subjects research. These seminars are designed to provide education and communicate information related to human subject's research, and to enhance the effectiveness of processes and operational procedures within the research program.

(c) **IRB- and Office of Clinical Research-sponsored training:** The STVHCS participates with the UTHSCSA in providing an 8-hour training course on "Conducting Clinical Research". All personnel involved in human subject's research at the STVHCS are strongly encouraged to participate in this course, which is offered 3 times per year. The UTHSCSA IRB also provides periodic Forums for education of investigators and their research staff related to human subjects research issues.

(d) **Investigator Handbook:** The STVHCS Investigator Handbook is available in text form and on the STVHCS research website to serve as a practical guide to assist research teams in following policies, regulations, and laws to protect the rights and welfare of human participants. The Investigator Handbook provides information regarding where investigators can go to find more information or to have questions addressed.

(e) **Individualized training:** The R&D Office staff, the ACOS/Research, and the Assistant to the ACOS/Research for Clinical Research are readily available to provide individualized training and facilitation of the responsible conduct of human subjects research.

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(f) **Policies and Standard Operating Procedures (SOPs):** The policies and SOPs of the STVHCS R&D Office and UTHSCSA IRB are posted on their respective websites to facilitate their use by investigators and their research staff.

(2) **Educational outreach to research participants:** The STVHCS recognizes that people who understand research will be better protected as research subjects. Therefore, a program of educational outreach is in place to improve the understanding of research in the community. This includes the display of posters and pamphlets in public areas of the STVHCS, providing community speakers to discuss VA research when the opportunity arises, and maintaining a STVHCS research website that is accessible to the public. Past, current, or prospective participants in research have the opportunity to pose questions, concerns, complaints, or suggestions to investigators, the R&D Office, and the IRB through the required contact information provided in the Informed Consent document, and listed on posted pamphlets and posters.

(3) **Compliance plan: (I.1.A)** The Compliance Office has developed and implemented a plan to evaluate and monitor compliance to human subjects regulations and guidelines. This is detailed in the STVHCS Policy Memorandum 003-08-01 (Attachment H). The Research Compliance Office has the following responsibilities:

(a) Annually reporting to the R&D Committee an evaluation (based on audits, compliance assessments, and quality improvement activities) of the committee's performance, and that of its subcommittees, including the IRB, with regard to compliance with established policies and procedures. This evaluation will provide a determination of the STVHCS's compliance with research subject protection requirements and assurance that all committees are fulfilling their role in meeting the program objectives.

(b) Conducting periodic audits of IRB composition, operational procedures, and compliance with applicable regulations where they concern VA protocols.

(c) Conducting random, select, and for-cause audits of protocols, to include: evaluation of research procedures and adherence to the approved protocol; documentation of research activities in the medical record; adherence to the approved Scope of Practice of all research personnel; completeness and accuracy of regulatory and subject binders, case report forms, and source documents; adequacy of both the informed consent document and the informed consent process, including its documentation; and evaluation of any other process or procedure that has bearing on the responsible conduct of human subjects research. The STVHCS and UTHSCSA Compliance Offices are closely aligned, and communicate to the reciprocal office any findings that have bearing on the protection of human subjects at either institution.

(d) Reviewing and evaluating reports by the IRB related to VA research.

(4) **Procedures for addressing research-related complaints and concerns, and allegations and findings of research non-compliance:**

(a) **Complaints, concerns, or allegations related to research:** The STVHCS HRPP maintains an open door policy. Any individual is welcome to contact the research office or any other component of the HRPP with a question, concern, complaint, comment, or suggestion. All Informed Consent documents must contain the contact information for the IRB so that a research subject may bring any questions, concerns, complaints, comments, or suggestions to the attention of the IRB, who will in turn communicate those to the ACOS for R&D as appropriate. The ACOS for R&D is responsible for

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insuring that complaints, concerns, or allegations related to research are reviewed and appropriate actions are taken. The process for reviewing and addressing complaints, concerns, or allegations related to research is detailed in Research Service Standard Operating Procedure 08-26.

(b) **Findings of research non-compliance:** Research non-compliance may be identified through self-reporting by a principal investigator, receipt and subsequent review of an allegation by the ACOS for R&D, or through a routine or for-cause audit of a research protocol by the compliance office. Potential research non-compliance involving human subjects research will be immediately reported to the IRB, who will take appropriate actions as outlined in UTHSCSA IRB Policy. Findings of the IRB will be reported to the investigator, the ACOS for R&D, the R&D Committee, and the Medical Center Director. The final course of action regarding the complaint or allegation is entirely dependent upon the nature, severity, and degree of seriousness of the findings. All actions taken shall be at the institutional level most appropriate for the circumstances.

(c) **Reporting of research non-compliance:** The IRB Director, or ACOS/R&D through the Medical Center Director as the Institutional Official for the HRPP, will report all actions requiring reporting to regulatory bodies outside the medical center, such as the Regional Office of Research Oversight (ORO), VHA Information Security Officer (ISO) if information security is at issue, Office for Human Research Protections (OHRP), the Food and Drug Administration (FDA) if investigational devices or drugs are involved, and/or any other federal agencies overseeing research who require separate reports from OHRP. If the noncompliance is related to VA-funded research, it will also be reported to the VA Office of Research and Development. Reports shall be made as soon as possible after recognition of a reportable event and within the maximum allowable time required by the applicable regulatory body. Instances that may require such notification, include: findings of serious or continuing noncompliance with the regulations for the protection of human subjects or with the requirements of the IRB; any unanticipated problems involving risks to subjects or others (e.g., death of healthy volunteers participating in research); and suspension or termination of IRB approval (e.g., associated with unexpected harm, research not being conducted in accordance with the IRB's requirements).

### **(5) Monitoring and reporting of unanticipated problems and adverse events**

(a) **Reporting to the IRB:** The purpose of reporting unanticipated problems involving risk to subjects or others is to protect the rights and welfare of participants in human subject research. Investigators involved in human subject research at the STVHCS are required to promptly report all unanticipated problems involving risk to subjects or others (UPIRSO). UPIRSO are unanticipated AND possibly related events/problems that represent a greater risk to subjects or others. For those that involve physical or psychological harm (also known as adverse events), if they are serious and unanticipated and possibly related to the study, they should also be considered to be a UPIRSO, and should be reported to the IRB within 7 days of the PI becoming aware for internal (under the jurisdiction of the UTHSCSA IRB) or 14 days if external (not under UTHSCSA IRB jurisdiction). All internal UPIRSO events that are life threatening or fatal should be reported within 48 hours. All others should be monitored by the investigator/data safety monitoring board, reported promptly if together they rise to the definition of UPIRSO, or summarized with all adverse events and unanticipated problems in the next Continuing Review report. UPIRSOs that involve the loss or compromise of individually identifiable information of a research subject should also be reported promptly to the Privacy Officer. UPIRSOs that involve the violation of information security requirements should also be reported promptly to the Privacy Officer.

(b) **Evaluation by the IRB:** All reports will be reviewed with due consideration for whether risks to subjects are still minimized and reasonable in relation to the anticipated benefits, if any, to the

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subjects and the importance of the knowledge that may reasonably be expected to result. The review process, as detailed in UTHSCSA IRB Policy involves initial review by the IRB chairperson or designated reviewer(s); the convened IRB, if appropriate; and reporting to the appropriate institutional official(s).

(c) **Reporting to the STVHCS:** Effective communication between the UTHSCSA IRB and STVHCS research program is essential to the function of the HRPP of the STVHCS. The ACOS for R&D, or the Assistant Chief for Clinical Research should the ACOS for Research and Development be unavailable, is the point of contact for all communications from the IRB. The procedures for effective communication between the IRB and STVHCS are detailed in the Research Service Standard Operating Procedure 08-37.

(d) **Reporting to regulatory agencies:** The IRB Director, or ACOS/R&D through the Medical Center Director as the Institutional Official for the HRPP, will report all UPIRSOs to external regulatory agencies, such as the Regional Office of Research Oversight (ORO), VHA Information Security Officer (ISO) if information security is at issue, VHA Privacy Officer if the privacy/confidentiality of a research subject was compromised, Office for Human Research Protections (OHRP), the FDA if investigational devices or drugs are involved, and/or any other federal agencies overseeing research who require separate reports from OHRP. If the UPIRSO is related to VA-funded research, it will also be reported to the VA Office of Research and Development. Reports shall be made as soon as possible after recognition of a reportable event and within the maximum allowable time required by the applicable regulatory body.

(6) **Expiration of research protocol approval:** Approval for a research protocol may expire because of failure to meet reporting (e.g. Continuing Review) deadlines. In this case, the Principal Investigator will be notified that activities related to the research protocol must immediately cease, with the exception of those activities that are determined by the IRB or IRB Chair, in consultation with the Chief of Staff, to be required to ensure the safety of subjects already enrolled in the protocol. In this case, the IRB will notify investigators to immediately submit a list of participants for whom stopping research activities would cause harm. The expiration in approval of the protocol will be updated upon receipt and satisfactory review and approval of the required documentation by the IRB and R&D Committee.

(7) **Suspension or termination of a research protocol:** The STVHCS Director, IRB, R&D Committee, and/or the ACOS for R&D as the designated representative of the STVHCS Director, have the independent authority to suspend or terminate a research protocol at the STVHCS that is not being conducted in accordance with IRB or R&D Committee requirements, or is associated with unexpected harm to subjects. Demonstration of a pattern of repeated failure to comply with reporting or training deadlines by the Principal Investigator or his/her staff will result in suspension of the study based on continuing research noncompliance. Suspensions or terminations must be reported to the appropriate oversight agencies.

(8) **Oversight of External Research Study Monitors:** The evaluation of STVHCS human subjects research by external research study monitors, from the research sponsor or other outside regulatory agency, will be monitored by the R&D Office and reported to the R&D Committee through the QA/QI Subcommittee. The Policies and procedures related to the conduct of external Research Study Monitors are detailed in Research Service Memorandum 151-08-11 and Research Service Standard Operating Procedure 08-40.

(9) **Annual evaluation of the HRPP:** With input from investigators, IRB members, the R&D Office, and Compliance Office, the R&D Committee will annually evaluate the allocated resources,

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implementation, performance, and improvement activities of the HRPP, and will communicate its findings and any recommendations to the Director.

(10) **Institutional Conflict of Interest:** The STVHCS has instituted policy and procedures to ensure that the welfare of human participants and the integrity of research will not be compromised, or appear to be compromised, by competing institutional interests or obligations. The policy and procedures are detailed in STVHCS Policy Memorandum 151-08-10 . Regional Counsel for the STVHCS will be consulted on questions related to Institutional Conflict of Interest.

m. **ACCREDITATION**—In accordance with VA Office of R&D requirements, the STVHCS will pursue AAHRPP accreditation, a program of independent external review of human research protection programs.

### 4. REFERENCES:

- a. Department of Health and Human Services (DHHS) Code of Federal Regulations Title 45, Public Welfare, Part 46, Protection of Human Subjects (45 CFR 46, 46.101)
- b. VA Code of Federal Regulations Title 38, Pensions, Bonuses, and Veteran's Relief, Chapter 1 Department of Veterans Affairs, Part 16, Protection of Human Subjects
- c. Code of Federal Regulations Title 21, Chapter 1 Food and Drug Administration (FDA) Department of Health and Human Services regulations pertaining to rights and welfare of human subjects participating in research involving investigational drugs and devices [21 CFR parts 50, 56, 312, 312.3, and 812, 812.3 (g), 812.3(r)]
- d. VHA Handbook 1200.5 Requirements for the Protection of Human Subjects in Research, dated July 15, 2003
- e. VHA Directive 2000-043, Banking of Human Research Subjects' Specimens, dated November 6, 2000
- f. VA Code of Federal Regulations Title 38, Pensions, Bonuses, and Veteran's Relief, Chapter 1 Department of Veterans Affairs, Part 17 Medical (38 CFR 17.33a, 17.45, 17.85, 17.92)
- g. STVHCS Policy Memorandum 151-08-02, Research and Development Committee, dated April 1, 2008
- h. STVHCS Policy Memorandum 119-08-05, Handling of Investigational Drugs, dated May 5, 2008
- i. STVHCS Policy Memorandum 119-08-21, Investigational Devices in Human Research, dated May 1, 2008
- j. Research Service Standard Operating Procedure 08-35, Protection of VA-sensitive Research Information, dated May 2, 2008
- k. VHA Handbook 1200.8, Safety of Personnel Engaged in Research, dated June 7, 2002
- l. STVHCS Policy Memorandum 151-07-06, Research Misconduct, dated April 17, 2007
- m. VHA Handbook 1058.2, Research Misconduct, dated May 4, 2005
- n. VHA Directive 2003-031, Establishment of a Facility Human Protection Program, dated June 13, 2003

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o. STVHCS Policy Memorandum 003-08-01, attachment H, CBI Human Research Protection Program

p. Research Service Standard Operating Procedure 08-26, Human Subject Concerns / Complaints/ Allegations of Research Improprieties, dated April 1, 2008

q. Research Service Standard Operating Procedure 08-37, Correspondence and Communication between Components of the Human Research Protection Program and Regulatory Agencies, dated April 1, 2008

r. Research Service Standard Operating Procedure 08-40, External Clinical Research Monitoring Visits, dated February 29, 2008

s. STVHCS Policy Memorandum 151-08-11, Oversight of External Clinical Research Monitoring Visits, dated April 1, 2008

t. STVHCS Policy Memorandum 151-08-10, Managing Institutional Conflict of Interest, dated May 2008

u. Department of Health and Human Services (DHHS) Code of Federal Regulations Title 45, Public Welfare, Parts 160 and 164, Standards for Privacy of Individually Identifiable Health Information and Security Standards for the Protection of Electronic Protected Health Information

**5. RESPONSIBILITY:** Associate Chief of Staff for Research and Development (151)

**6. RESCISSION:** STVHCS Policy Memorandum 151-07-03, dated April 17, 2007

**7. RECERTIFICATION:** June 2011

(original signature on file)

**RICHARD J. BALTZ**  
Center Director

Attachment

DISTRIBUTION: A

## DETERMINING WHETHER AN ACTIVITY IS HUMAN RESEARCH

1. In accordance with federal and institutional regulations and prior to project implementation, the IRB must approve any undertaking in which STVHCS staff conducts non-exempt human research. This Appendix supplements the STVHCS Human Research Protection Program Policy (PM 151-08-03) by providing additional information related to determining whether an activity is research involving human participants and covered by the Federal Regulations. In general, any activity that meets either the Department of Health and Human Services (DHHS) definition of both “research” and “human subjects” or the Food and Drug Administration (FDA) definitions of both “clinical investigation” and “human subjects” is considered human research and requires review and approval by the IRB.

2. It is the responsibility of each investigator to seek IRB approval prior to initiation of any non-exempt research involving human subjects or before conducting any clinical investigation. The investigator is responsible for making a preliminary decision regarding whether his/her activities meet either (a) the Department of Health and Human Services (DHHS) definitions of both “research” and “human subjects” or (b) the FDA definitions of both “clinical investigations” and “human subjects”. A worksheet titled “Determining Whether An Activity is Research Involving Human Participants” is also available on the UTHSCSA IRB website (<http://research.uthscsa.edu/irb/sop.shtml>) to guide the investigator in making this decision. The investigator may also contact the STVHCS R&D Office, the UTHSCSA OIRB staff, the IRB Chair, or IRB members for advice on the application of the federal regulations and local policy. The following sequential assessment is used when evaluating a particular activity to determine whether the activity is human research:

a. **Step 1:** Is the activity “Human Research” according to DHHS regulations?

(1) **Criterion 1**--the activity is research if either of the following is true:

(a) It is part of a systematic investigation (including research development, testing and evaluation) to test a hypothesis and permit conclusions to be drawn, usually described in a formal protocol that sets forth an objective and a set of procedures designed to reach that objective; or,

**NOTE:** *It is designed to (e.g., the primary purpose) contribute to generalizable knowledge (expressed, for example, in theories, principles, and statements of relationships, or published in medical journals as research)*

(b) If either (1) or (2) are true, proceed to criterion 2.

(c) If neither (1) nor (2) are true, the activity is not “Human Research” according to DHHS regulations. Go to Step 2 to determine whether the activity is “Human Research” according to FDA regulations.

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(2) **Criterion 2.** The research involves human participants because:

(a) The investigator will obtain data about living individuals; and

(b) The investigator will obtain this data through intervention or interaction with those participants; or

(c) The information obtained by the investigator is both private (i.e., the information is private because it includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public) AND identifiable (i.e., the information is individually identifiable because the identity of the participant may be readily ascertained by the investigator or associated with the information.).

(d) If the statements in criterion 2 are true, the activity is human research according to DHHS regulations. Go to Step 2 to determine whether the study is human research according to the FDA regulations.

(e) If the statements in criterion 2 are not true, the activity is not human research according to DHHS regulations. Go to Step 2 to determine whether the study is human research according to the FDA regulations.

**b. Step 2:** Is the activity “Human Research” according to FDA regulations?

(1) **Criterion 1.** The activity involves an FDA regulated test article because at least one of the statements below is true:

(a) The activity involves the use of a drug, other than the use of a marketed drug in the course of medical practice; or

(b) The activity involves the use of a device to evaluate safety or effectiveness of that device; or

(c) Data from the activity will be submitted to, or held for inspection by, the FDA in support of a marketing or research application for an FDA-regulated product.

(d) If any of the above is true, proceed to criterion 2.

(e) If none of the above is true, then the activity is not Human Research according to FDA regulations.

(2) **Criterion 2.** The activity involving an FDA-regulated test article involves human participants because at least one of the statements below is true:

(a) The test article will be used on one or more humans; or

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(b) The data obtained from controls will be submitted to, or held for inspection by the FDA in support of a marketing or research application for an FDA-regulated product; or

(c) The data obtained from use of a device on tissue specimens will be submitted to, or held for inspection by, the FDA in support of a marketing application or research application for an FDA regulated product.

(d) If any of the above is true, the activity is human research according to FDA regulations.

(e) If none of the above is true, then the activity is not Human Research according to FDA regulations.

**c. Step 3: Summary of “Human Research” determinations (DHHS & FDA)**

(1) DHHS—If the activity is considered research (Step 1, criterion 1) and involves human participants (Step 1, criterion 2), it is considered human research according to the DHHS and requires IRB approval.

(2) FDA—If the activity involves an FDA regulated test article (Step 2, criterion 1) and involves human participants (Step 2, criterion 2), it is considered human research according to the FDA and requires IRB approval.

**3. The following are examples of human subject research studies that must be reviewed and approved by the IRB.**

**a. Masters thesis/Doctoral dissertation:** graduate work which involves research on human subjects or a clinical investigation and results in a thesis or dissertation.

**b. Pilot studies:** pilot studies involving human subjects are considered human subject research and require IRB review.

**c. Clinical research:** involves research to increase scientific understanding about normal or abnormal physiology, disease states or development and research to evaluate the safety, effectiveness or usefulness of a medical product, procedure, or intervention. Vaccine trials, medical device or drug studies and cancer research are all types of clinical research.

**d. Behavioral and Social Sciences Research:** 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.

**e. Epidemiological Research:** focuses on health outcomes, interventions, disease states and conclusions about cost-effectiveness, efficacy, efficiency, interventions, or delivery

of services to affected populations. This research may be conducted through surveillance, observation monitoring, and reporting programs. Other methods are retrospective review of medical, public health and/or other records.

**f. Human Genetic Research:** includes studies such as pedigree studies, positional cloning studies, gene transfer research, longitudinal studies to associate genetic conditions with health, health care or social outcomes and gene frequency studies.

**g. Repository or Bank:** includes collecting or storing human specimens or data for future use in research.

**4. The following activities are generally not considered “research” and do not need IRB approval:**

**a. Health surveillance.** Health surveillance is an ongoing part of the medical care and public health care functions closely integrated with timely dissemination of these data to those responsible for preventing and controlling disease or injury (may include emergent or urgently identified or suspected imminent health threats to the population to document the existence and magnitude).

**b. Routine Quality Improvement** (QI) means systematic, data-guided activities designed to bring about immediate, positive changes in the delivery of health care in particular settings. QI involves deliberate actions to improve care, guided by data reflecting the effects of local care (e.g., types of practical problem solving; an evidence-based management style; the application of science of how to bring about system change; review of aggregate data at the patient/provider/unit/ organizational level to identify a clinical or management change that can be expected to improve care).

**c. Medical quality assurance.** This refers to activities particular to an institution’s Quality Assurance (QA) program, such as those activities protected from disclosure by the Department of Veterans Affairs as part of its confidential medical quality-assurance program or other equivalent programs. (e.g., see VHA Directives or equivalent university or institutional policy)

**d. Program evaluation.** This refers to assessments of the success of established programs in achieving objectives when the assessments are for the use of program managers, for example, a survey to determine if program beneficiaries are aware of the availability of program services or benefits. [Note: Non-research evaluation is generally designed to assess or improve the program or service rather than to generate knowledge about a disease or condition.]

**e. Customer satisfaction surveys or interviews.** This refers to surveys of program users to obtain feedback for use by program managers, and is similar to program evaluation. The purpose of these surveys is to improve a specific service or program or develop new services or programs under the control of the individual/organization obtaining the information and not to conduct research.

f. **Class Projects**: academic projects or student assignments involving collection of data from human subjects when the data is used solely for the purpose of teaching course content (e.g., to teach proficiency in performing certain tasks or using specific tools or methods) and not intended to be used to develop or contribute to generalizable knowledge.

g. **Case Reports**: use of medical information collected from a clinical activity rather than a research activity and presented on no more than three (3) patients. Case reports are generally done by retrospective review of the medical record and highlights a unique treatment, case or outcome. The examination of the case is usually not systematic and there is usually no data analysis or testing of a hypothesis. Investigators must ensure that the HIPAA privacy rules are followed with respect to using or accessing PHI (a HIPAA authorization or waiver may be required).

h. **Biography or oral history of a single individual**: research involving a single individual is not generalizable knowledge. (see precautions in case reports)

i. **Publicly Available Data**: research involving publicly available information (e.g., census data, labor statistics) does not constitute human research.

**6. The following research is generally not considered “human research” and do not need approval:**

a. **Repository Research, Tissue Banking, and Databases**: research limited to obtaining stored data or specimens from a repository only if the investigator cannot readily ascertain the identity of the subject from whom the data or materials originated.

b. **Anonymous Pre-existing Data Sets or Specimens**: anonymous pre-existing data or specimens (anonymous materials are those with no personally identifiable information contained in either the original data or attached to the original specimen).

c. **Coded pre-existing or coded prospective data or specimens**: if 1) the private information/specimens were not/will not be collected specifically for the currently proposed research through an interaction or intervention with living individuals, or 2) the investigator(s) never obtains identifiable data/specimens because: a) the holder of the key to decipher the code, destroys the key before the data is provided to the investigator, or b) the investigators and the holder of the key enter into an agreement prohibiting the release of the key to the investigators under any circumstances, or until the individuals are deceased; or c) there are laws or IRB-approved written policies for a repository/data management center that prohibit the release of the key to the investigators under any circumstances, until the individuals are deceased.