



**Department of Veterans Affairs
Northern California Health Care System**

Research Service

HUMAN RESEARCH PROTECTION PROGRAM

Standard Operating Procedures (SOP)

R&D Approval Date: July 18, 2018

Effective Date: July 16, 2014

Contents

1. PURPOSE..... 3

2. SCOPE..... 3

3. DEFINITIONS 3

4. ELEMENTS OF THE VANCHCS HUMAN RESEARCH PROTECTION PROGRAM
(HRPP):..... 7

5. APPLICABLE ASSURANCES: 7

6. RESPONSIBILITIES: 8

7. PROCEDURES 13

8. REFERENCES 14

9. SIGNATURE BLOCK 14

1. PURPOSE

This policy describes the Human Research Protection Program (HRPP) at the VA Northern California Health Care System (VANCHCS). The HRPP is an integrated, systematic and comprehensive program with dedicated resources to protect the human rights, safety and well being of any individual who may serve as a subject of an experiment in VANCHCS. The HRPP is based on the Belmont Report, the document of ethical principles underlying modern concepts of human subject protection. The three key principles governing the use of humans in research at the VANCHCS are respect for persons, beneficence and justice. A number of procedures must be followed to ensure that participation is voluntary, that the subject understands the nature of the proposed experiment and the risks and benefits (if any), and that the subject's privacy is protected.

2. SCOPE

This policy applies to all research involving human subjects, and all other activities which even in part involve such research, regardless of whether the research is otherwise subject to VA regulation, if:

- a. The research is sponsored/funded by the VA through VANCHCS; or
- b. The research is conducted completely or partially in VANCHCS facilities; or
- c. The research is conducted in approved off-site locations and/or facilities; and/or
- d. The research is conducted by VANCHCS investigators while on official VA duty time.

All research to be performed on human subjects (normal volunteer, abnormal volunteer, outpatient, inpatient, non-patient in the Health Care System or elsewhere, etc.) at VANCHCS requires the prior approval of the Research and Development (R&D) Committee.

The R&D Committee will review studies involving human research only after thorough review by the Human Studies Subcommittee/Institutional Review Board (IRB), at VANCHCS.

3. DEFINITIONS

a. ADVERSE EVENT (AE): Any untoward event associated with a research study. The event does not necessarily have a causal relationship with treatment or study intervention. An AE can be any unfavorable and unintended sign, symptom or disease.

b. ASSURANCE: See FEDERALWIDE ASSURANCE (FWA). The FWA replaces all other previous forms of assurance, i.e., MPA, SPA, VA MPA, etc.

c. BENEFICENCE: Beneficence is understood as an obligation. Two general rules have been formulated as complementary expressions of beneficent actions in this sense:

(1) Do not harm and

(2) Maximize possible benefits and minimize possible harms.

d. CONSENT FORM: Except where noted in this Policy Statement, the term "consent form" is understood to consist of a completed "VA RESEARCH CONSENT FORM" (VA Form 10-1086) submitted to and approved by the R&D Committee and its appropriate subcommittees for the specific protocol prior to the performance of that research. This form must be signed by three individuals: the subject, a witness (other than the Principal Investigator), and by the Principal Investigator.

e. CONTINUING REVIEW: Periodic review by the Institutional Review Board (IRB) 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. See also ONGOING MONITORING.

f. 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. The FWA replaces all other previous forms of assurance, i.e., MPA, SPA, VA MPA, etc. All VA facilities conducting human research will be required to maintain an FWA.

g. FOOD AND DRUG ADMINISTRATION (FDA): The Federal agency responsible for the regulation of food, drugs and cosmetics, including the human subject research performed for FDA-regulated articles.

h. 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, i.e., academic affiliate or another VA Medical Center, by the organization.

i. HUMAN SUBJECT: A living individual about whom a research investigator (whether professional or student conducting research) obtains:

(1) Data through intervention or interaction with the individual [Intervention includes both physical procedures by which data are gathered (for example, venipuncture) 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.], or

(2) Identifiable private information [Private information 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 (for example, a medical record). In order to obtain information to perform research involving human subjects, private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information)].

j. HUMAN SUBJECT RESEARCH: Human subject research includes all research meeting the definition of “research” performed with “human subjects.”

k. 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 R&D Committee. Other committees with the same or similar functions are also considered to be IRBs.

l. INVESTIGATIONAL DEVICE EXEMPTION (IDE): The process by which the FDA permits a device that otherwise would be required to comply with a performance standard or to have premarket approval to be shipped lawfully for the purpose of conducting investigations of that device.

m. INVESTIGATIONAL NEW DRUG APPLICATION (IND): The process by which new drugs or biologics, including the new use of an approved drug, are registered with the FDA for administration to human subjects. An IND number is assigned by the FDA to the drug or biologic for use in tracking.

n. JUSTICE: Justice is the consideration of who ought to receive the benefits of research and bear its burdens, in the sense of "fairness in distribution" or "what is deserved." An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly.

o. IRB DOCUMENTATION: Any written evidence of the IRB’s consideration, evaluation, and/or assessment of proposed or active research.

p. LEGALLY AUTHORIZED REPRESENTATIVE: An individual, judicial or other body, authorized under applicable law to consent on behalf of a prospective subject to the subject’s participation in the procedure(s) involved in research.

q. 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 facility to delineate the terms and conditions under which it may utilize another entity’s IRB.

r. MINIMAL RISK: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

s. NON-VETERAN RESEARCH SUBJECTS: 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 pertain to non-veteran subjects enrolled in VA approved research.

t. ONGOING MONITORING: Review by the IRB of such information as adverse event reports, protocol amendments, reports of protocol deviations, and other information about ongoing research studies, during the period for which the protocol is approved.

u. PRINCIPAL INVESTIGATOR: An individual who conducts an 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.

v. PROTOCOL: A plan that includes, at a minimum, the objectives, rationale, design, methods and other conditions for the conduct of a research study.

w. RESEARCH: A systematic investigation, including development, testing and evaluation, designed to develop or contribute to generalizable knowledge. Activities that meet this definition constitute research for purposes of this policy, whether or not they are conducted or supported under a program that is considered research for other purposes. For example, some demonstration and service programs may include research activities. See also VA RESEARCH.

x. RESPECT FOR PERSONS: Respect for persons incorporates at least two ethical convictions: first, that individuals should be treated as autonomous agents, and second, that persons with diminished autonomy are entitled to protection. The principle of respect for persons thus divides into two separate moral requirements: the requirement to acknowledge autonomy and the requirement to protect those with diminished autonomy.

y. SAFETY REPORTS (IND/IDE): These are written reports from sponsors that notify the FDA and all participating investigators of any adverse experience associated with the use of a drug that is both serious and unexpected.

z. SERIOUS ADVERSE EVENT (SAE): Any 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.

aa. 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.

bb. UNEXPECTED ADVERSE EVENT: Events that occur in a frequency or severity greater

than described in the investigator's brochure or any adverse event that has not previously been observed, e.g., included in the investigator brochure.

cc. VA RESEARCH: All research and all other activities which even in part involve such research, regardless of whether the research is otherwise subject to VA regulation, if the research falls under the criteria described in this policy section "2. SCOPE."

dd. VULNERABLE SUBJECTS/POPULATION: Individuals whose willingness to volunteer in a research study may be unduly influenced or coerced and individuals with limited autonomy. These individuals may include, but are not limited to, children, prisoners, pregnant women & fetuses, mentally disabled and those with impaired decision-making capacity, or economically and/or educationally disadvantaged persons.

ee. ClinicalTrials.gov: the National Library of Medicine's (NLM) public registry, ClinicalTrials.gov. ClinicalTrials.gov provides patients, family members, health care professionals and members of the public easy access to information on clinical trials for a wide range of diseases, conditions and health problems.

4. ELEMENTS OF THE VANCHCS HUMAN RESEARCH PROTECTION PROGRAM (HRPP):

The administrative component of the HRPP, at a minimum, consists of the following involved individuals: the VANCHCS Director, Chief of Staff, Research Compliance Officer, Associate Chief of Staff for R&D, Administrative Officer for R&D, and the HRPP Manager/Administrator.

The HRPP at VANCHCS comprises three arms. These are:

a. Institutional review, both initial and continuing, of all research involving human use: This responsibility for review and oversight is accomplished by the IRB through the R&D Committee. (See R&D SOP manual)

b. Education: There is a program ensuring that investigators, research staff, IRB members and other individuals with responsibility for human subject protection have completed required training in human subject use and protection.

c. Compliance and Quality Improvement: There is an ongoing program evaluating HRPP effectiveness, including quality improvement activities. Evaluation and improvement include measuring, assessing and improving compliance with institutional HRPP policies, assurances and other requirements for the protection of human subjects in research.

5. APPLICABLE ASSURANCES:

45 CFR 46 section 103(a) requires that each institution engaged in Federally –supported human subject research file an "Assurance" of protection for human subjects. The Assurance formalizes the institution's commitment to protect human subjects.

VANCHCS, as part of its Federal-Wide Assurance (FWA) numbered,

- a. FWA00001687: Issued to VA Northern California Health Care System,
- b. FWA00001294: Issued to East Bay Institute for Research and Education, Inc., a VA affiliated non-profit corporation.

VANCHCS has agreed to protect the welfare of all human subjects involved in research, whether or not the research is conducted or supported by a federal department or agency. Therefore, the VANCHCS IRB has oversight of all human research conducted at VANCHCS, or by its employees or agents.

Information contained in these FWAs is further refined by procedures delineated in VA Central Office and VANCHCS manuals, handbooks, memoranda, and Standard Operating Procedures documents, as well as, various other documents reflecting institutional culture.

6. RESPONSIBILITIES:

a. The Director will:

(1) Apply for, receive, and maintain an Assurance of Compliance with DHHS, OHRP (FWA). The Director is the VA's Federalwide Assurance Signatory Official and is ultimately responsible for oversight of human subject protection for VANCHCS. Such oversight is accomplished through membership on the R&D Committee, regular communication with the Chief of Staff and ACOS for Research and Development, HRPP Manager/Administrator, and ongoing communication with members of the research community.

(2) Review and approve VANCHCS Policy Statements and Standard Operating Procedures that include, at a minimum:

(a) Specific requirements for the membership and operation of the IRB to review research in compliance with VA regulations.

(b) The respective responsibilities of the institution and the IRB for human subject protection.

(c) The scope of activities delegated to the IRB.

(d) The method, frequency and nature of reporting to the R&D Committee.

(e) The process by which the institution evaluates the IRB's performance.

(3) Apply for, receive, and maintain accreditation of its HRPP.

(4) Provide sufficient resources for the HRPP, including the R&D Committee, SRS and IRB.

(5) Engage in a systematic budgeting process for the HRPP resources including personnel, materials, space, equipment, training and education. Budgeting includes consideration of the following factors:

(a) Analysis of the volume of research to be reviewed.

(b) Feedback from IRB members and staff.

(6) In consultation with the Chief of Staff, Associate Chief of Staff, the IRB and R&D Committee Chair and Program Manager, the Director will establish the appropriate number of IRBs, taking into consideration the volume, workload distribution, frequency of meeting, length of meetings, type of human research conducted at the institution, and the need for timely and thorough review. This assessment is conducted annually.

(a) The IRB Committee is appointed by the Director as the Campus Committee. As such, the IRB Committees serves the entire VANCHCS campus, and any institution for which the VANCHCS is designated as the IRB of Record.

(b) VANCHCS presently designates two (2) OHRP-registered IRB Committee.

1. IRB0000615 – VA No California Hlth Care System IRB#1

2. IRB00006332 – Veterans Hlth Administration Central Ofc IRB#1

(7) Assures that the Medical Center will provide necessary medical treatment to a research subject injured as a result of participation in a research project approved by the R&D Committee and conducted under the supervision of one or more VA employees

(a) Will adhere to the terms of the CRADA, to provide the necessary care of the injured subject.

(b) Will contract for needed care if the VANCHCS is not capable of furnishing economic care or is not capable of furnishing the care or services required

(c) If inpatient care must be proved to a non-veteran the Director may contract for such care

(d) Shall proved reasonable reimbursement for the emergency treatment of a research subject in a non-VA facility.

(8) Prohibits usurping IRB, SRS and R&D Committee Approval Authority or using undue influence. The Director prohibits VANCHCS officials, investigators, and employees, and sponsors contracting with EBIRE for research from:

(a) Maintaining or claiming IRB, SRS and/or R&D Committee approval of research that has been disapproved or not yet been reviewed by the IRB, SRS and/or R&D Committee.

(b) Attempting to use or using undue influence with the IRB, SRS and/or R&D Committee, any of its members or staff, an investigator or any other member of the research team to obtain a particular result, decision or action.

“Undue influence” means attempting to interfere with the normal functioning and decision-making of an oversight committee or to influence an committee member or staff, a investigator or any other member of the research team outside of established processes or normal and accepted methods, in order to obtain a particular result, decision or action by the oversight committee or one of its members or staff.

An individual who believes he or she has been subjected to such undue influence should make a report of non-compliance (e.g., to the Research Compliance Officer or Associate Chief of Staff, Research). Such reports will be reviewed in the same manner as reports of non-compliance.

(9) Ensuring VANCHCS HRPP obtains accreditation from an organization approved by ORD.

b. The Chief of Staff (COS) has overall responsibility for all clinical and academic activities of VANCHCS, including research.

c. The Research Compliance Officer (RCO) is responsible for developing, implementing, maintaining, and providing leadership, strategic direction and oversight of compliance and training activities for the Research Program; and ensures regulatory and policy updates are disseminated to investigators and research staff in a timely manner, performs ongoing monitoring of all areas of research compliance and acts decisively on issues of potential non-compliance.

d. The Associate Chief of Staff for Research and Development (ACOS for R&D) is responsible for management and oversight of the research enterprise of the VANCHCS. As such, this person will:

(1) Implement the HRPP policy, including the designation of a Human Research Protection Program Manager Administrator.

(2) Review and evaluate the reports and results of compliance assessment and quality improvement activities.

(3) Implement needed improvements and follow-up on actions as appropriate.

(4) Monitor changes in VA and other federal regulations and policies that relate to human research protections.

(5) Maintain accurate, up-to-date records regarding the mandatory training and

certification of investigators and other appropriate research staff in the protection of human research subjects as required by the ORD, VACO.

(6) Submitting, implementing, and maintaining an approved FWA through the Medical Center Director and the Office of Research Oversight (ORO) and to the Office of Human Research Protections (OHRP).

e. The Administrative Officer for Research and Development (AO for R&D) supervises the day-to-day operations of the Research Office. The AO is expected to be knowledgeable of Federal-wide requirements provided in the regulations for conducting human studies research.

f. HRPP Manager/Administrator is designated as OHRP's primary institutional contact person and has administrative responsibility for the HRPP.

The HRPP Manager/Administrator is responsible for:

(1) Renew OHRP IRB Registration every 3 years, and update IRB Registration through ORO within 30 days of any change to the IRB roster or other parts of the registration.

(2) Record Keeping and Reporting

(a) Ensure maintenance and accessibility of IRB records

(b) For federally supported research, provides certification of IRB approval for forwarding to appropriate federal agencies/departments

(c) Ensure reporting to the IRB of proposed changes in research activity and ensure appropriate initiation of changes

(d) Ensure prompt reporting to IRB, appropriate institutional officials, OHRP and any sponsoring federal department or agency head of unanticipated injuries, noncompliance or suspension/terminations of IRB approval for research

(3) Communication and Education

(a) Ensure constructive communication among research community (investigators, the IRB, and other staff involved in research)

(b) Provide ready access and consultation of regulations, policies and guidelines (facility's FWA, applicable VA policies, and other related federal regulations, as well as human subject protection policies and procedures)

(c) Fulfill all educational requirements mandated by VA ORD and OHRP in order to establish and maintain a culture of compliance with federal regulations and institutional policies relevant to the protection of human subjects.

(d) Serve as individual to whom research subjects and others may ask questions or voice research-related concerns or complaints. All concerns or complaints will receive a response, including investigation and appropriate remedial action if necessary.

(e) Serve as the institutional staff member who receives communication from federal agencies such as FDA or OHRP. These communications must be forwarded to the ACOS/R&D and the facility Director.

(4) Monitoring and Oversight

(a) Monitor reports provided by the Research Compliance Officer

(b) Ensure oversight mechanisms are implemented

g. The Research and Development Committee (R&D Committee) is the primary advisor to Executive Management on R&D issues and conducts oversight of the designated IRB. R&D Committee approval is required for all research conducted within the VA, by VA employees acting within the scope of their Government employment, or by using VA resources (including private, identifiable patient information). (See Policy Statement "R&D Committee," R&D SOP Manual.)

h. The Human Studies Subcommittee (Institutional Review Board) is responsible for initial and continuing review, approval, and monitoring of activities involving human use. The IRB shall promote respect for its advice and counsel in safeguarding the rights and welfare of human subjects; possess the professional competence necessary to review specific research activities; and facilitate the development and implementation of an educational plan for IRB members and investigators. [See Policy Statement "Institutional Review Board (Human Studies Subcommittee)," IRB SOP Manual)]

i. The Investigational Drug Service (IDS) is responsible for the safe use of drugs used in human research. The IDS implements all FDA regulations concerning investigational new drugs (INDs). The IDS receives all drugs used in research, maintains records accounting for the use of the drugs, monitors investigators' compliance with local and FDA requirements, and disposes of drugs at the end of the study.

j. The Pharmacy and Therapeutics Committee reviews and accepts R&D committee approval in any case in which an investigational new drug (IND) is to be administered. (See Policy Statement 119-3 "Consent of Patients for Use of Investigational Drugs" for the detailed consent requirements for investigational drug protocols.)

k. The Principal Investigator (the individual conducting the research) is the person with ultimate responsibility for the safety and welfare of research subjects. Included are the following responsibilities:

(1) Design of studies that are scientifically sound, and that minimize risks to subjects while

maximizing research benefits.

(2) Assuring that the research is conducted responsibly and in accordance with the IRB requirements.

(3) Assuring that research personnel are adequately trained and supervised.

(4) Disclosing potential conflict of interest.

(5) Reporting adverse events for a subject of the experiment to the appropriate authorities as required by the IRB.

(6) Ensuring adequacy of the informed consent document and process by obtaining the signed consent of the subject in the presence of a witness, and for complying with record keeping requirements.

(7) Maintaining and ensuring initial and ongoing approval for the research.

(8) Meeting education requirements for self and staff.

(9) Ensuring that all records of the research are maintained in such a form that the subject's privacy is protected and that no publication that may result from the research permits a participating subject to be identified.

(10) Register their clinical trial on ClinicalTrials.gov for the following:

(a) Clinical trials funded by an ORD research service (Clinical including Cooperative Studies, Health Services, and Rehabilitation) must be registered on ClinicalTrials.gov before funding will be released and prior to enrolling participants into their study. The PI (or project staff person) completes the clinical trial information on the ART Intranet site and submits to the ART Program.

(b) FDA regulated clinical trials of drugs and biologics, and devices.

l. The Quality Manager (QM) integrates the plans and findings of the RCO into the VANCHCS Quality Management Plan.

m. The Bioethics Advisory Functional Team (BAFT) advises the R&D Committee and IRB on ethical issues. If possible, IRB membership includes representation from the BAFT.

7. PROCEDURES

The VANCHCS HRPP procedures consist of multiple Policy Statements and Standard Operating Procedures. The Office of Research Administration has these procedures outlined in references such as the R&D Committee and IRB Standard Operating Procedures.

8. REFERENCES

38 CFR 16 “Protection of Human Subjects”

VHA HANDBOOK 1200.05 “Requirements for the Protection of Human Subjects”

VHA DIRECTIVE 2003-065 “Accreditation of Human Research Protection Programs”

VHA DIRECTIVE 2003-031 “Establishment of a Facility Human Protections Program”

Policy Statement “R&D Committee”

Policy Statement “Institutional Review Board (Human Studies Subcommittee)”

Policy Statement PS-119-3, “Consent of Patients for Use of Investigational Drugs”

VANCHCS R&D Committee Standard Operating Procedures

VANCHCS IRB Standard Operating Procedures

Section 801 of the Food and Drug Administration Amendments Act , Effective Date: October 1, 2007

9. SIGNATURE BLOCK

Dawn Schwenke, Ph.D., FAHA
Associate Chief of Staff for Research

Paramita Ghosh, PhD
Chair, Research and Development Committee