DEPARTMENT OF VETERANS AFFAIRS MEDICAL CENTER
San Francisco, California

MEDICAL CENTER MEMORANDUM No.11-19
February 20, 2015
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SUBJ: Human Research Protection Program (HRPP)

1. **PURPOSE:** To assure the safety and welfare of all human subjects enrolled in research projects sponsored or supported by this institution.

2. **POLICY:** All activities related to human subject research, regardless of funding source, will be guided by the ethical principles of respect for persons, beneficence and justice as outlined in the Belmont Report. The ethical conduct of research is a shared responsibility; it requires cooperation, collaboration and trust among the institution, investigators and their staff, the subjects who enroll in the research, and the members and staff of the HRPP.

3. **DEFINITIONS:**

a. A **Clinical Investigation** is research (as defined by VA or the Department of Health and Human Services, see 3.v) with human subjects (see 3.k).

1) An **FDA-regulated clinical investigation** is any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration (FDA) under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act (FFDCA), or need not meet the requirements for prior submission to the FDA under these sections of the FFDCA, but the results of which are intended to be later submitted to, or held for inspection by, the FDA as part of an application for a research or marketing permit.

2) The terms “research”, “clinical research”, “clinical study”, “study”, and “clinical investigation” are synonymous for purposes of FDA regulations.

b. **Conflict of Interest:** Personal or professional relationships, including financial investments, service on boards or committees, or concurrent obligations, that may affect a researcher’s ability to exercise independent judgment in the conduct of research.

c. **Collaborative Institutional Training Initiative (CITI):** The VA-approved human subjects research training provider.

d. **Collaborators** are individuals not based at the San Francisco

Veterans Affairs Health Care System (SFVAHCS) and have no direct or indirect authority to impact the research undertaken at this facility, and are therefore not subject to VA policies and educational requirements. Examples include statisticians under contract, colleagues at other institutions with whom de-identified data is shared, and researchers who retain VA services under the auspices of a subcontract or MOU.

e. **Clinical Research Office** (**CRO**): Consists of the Research Regulatory Coordinator (RRC), HRPP Coordinator(s), HRPP Regulatory Assistant(s) and administrative support staff.

f. The **Clinical Research Workgroup (CRW)** has been delegated the authority to review and recommend approval of clinical research by the Research and Development Committee (R&DC).

g. The **Department of Defense (DOD)** provides funding for research projects and has additional requirements for review and approval of those projects.

h. **Exempt Research:** Federal regulations define certain types of research as exempt from the regulations for human subjects research (see 38 CFR 16.101(b)).

i. **Generalizable knowledge** is information based on results or findings that are expected:

1) to be reproducible, and

2) apply broadly with the expectation of predictable outcomes.

j. **HRPP:** Consists of the SFVAHCS CRO, the Research Compliance Officer(s) (RCO), the Privacy Officer (PO) with responsibility for human research, the Information Security Officer (ISO) with responsibility for human research, the CRW, the Director of Research Operations (DRO), the Deputy Associate Chief of Staff for Clinical Research (D-ACOS/CR), the Associate Chief of Staff for Research (ACOS/R&D), and the Institutional Official (IO).

k. **Human subject**:

1) a living individual about whom an investigator conducting research obtains

a) data through intervention or interaction with the

individual or

b) identifiable private information (such as data or tissue); or

2) an individual, either a healthy person or a patient, who becomes a participant in research, either as a recipient of the test article or as a control.

l. A **Humanitarian Use Device** (HUD) is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 4000 individuals in the U.S. per year. A **Humanitarian Device Exemption** may be granted by the FDA in lieu of human subjects research approval for use of an HUD.

m. **Institutional Conflict of Interest:** Business agreements or relationships that may compete or appear to compete for the same resources within the institution. An Institutional Conflict of Interest might occur when research involves patents or royalties as the VA retains a portion of the earned income from those sources.

n. The **Institutional Official (IO)** is the SFVAHCS Medical Center Director (MCD).

o. **Institutional Review Board (IRB):** SFVAHCS's IRBs of record are UCSF's Committee on Human Research (CHR) and the Veterans Affairs Central Institutional Review Board (VA CIRB).

p. **International research**

1) **<u>is</u>** VA-approved research

a) conducted at international sites (not within the U.S., its territories, or Commonwealths);

b) using human biological specimens (identified, de-identified, or coded) or data (identified, de-identified, or coded) originating from international sites; or

c) that entails sending such specimens or data out of the U.S.

2) **<u>is not</u>**

a) a multisite trial where a VA facility is only one of the participating sites <u>unless</u>:

(1) VA is a sponsor;

(2) VA holds the Investigational New Drug (IND)

(3) VA manages the data collection and analyses;

(4) The PI for the total study is a VA investigator; or

b) research conducted at U.S. military bases, ships, or embassies

c) research that has been categorized as Exempt by the IRB

d) research involving use of secure remote access to data on VA servers within the U.S. or Puerto Rico.

q. **Investigational Drug:** A medication for which an investigational new drug application (IND) has been filed with the Food and Drug Administration (FDA).

r. **Investigational Device:** A device for which an investigational device exemption (IDE) has been filed with the Food and Drug Administration (FDA).

s. **Local serious adverse events (SAEs)** are those occurring at the SF VAMC, VA-leased space at UCSF Mission Bay, or affiliated VA research sites (e.g., CBOCs).

t. **Noncompliance** is defined as failure to adhere to the laws, regulations, or VA or University policies governing human research. **Continuing Noncompliance** is persistent noncompliance. **Serious Noncompliance** is defined as noncompliance (1) involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others, or (2) substantively compromising the effectiveness of the SFVAHCS's human research protection or human research oversight programs. The unfounded classification of a serious adverse event as "anticipated" also constitutes serious noncompliance. (See VHA Handbook 1058.01 for specific examples.)

u. **NCIRE – the Veterans Health Research Institute** is the SFVAHCS's non-profit organization.

v. **Research** is defined by the VA and the Department of Health and Human Services (DHHS) as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to

generalizable knowledge. VA further defines research as a systematic investigation designed to produce information to expand the knowledge base of a scientific discipline (or other scholarly field of study).

w. **Research Involving Human Subjects** is any activity that:

1) meets the definition of research (as defined by VA or DHHS) AND involves a human subject as described under paragraph k.1) above; or

2) meets the definition of a clinical investigation AND involves a human subject as described under paragraph k.2) above.

x. **Research sites:** While most research will be conducted at the SFVAHCS main campus, from time to time researchers may be engaged in research at one of our Community Based Outpatient Clinics (CBOCs) or at another facility with the approval of the R&DC.

y. **Research staff:** are those individuals who are engaged in research with human subjects that is approved (or pending approval) at this station, regardless of type of employment (VA-paid or WOC).

z. **Restricted Research:** Research that is prohibited at the VA or that requires special permission or approval. For example, research that involves the provision of in vitro fertilization or interventions with neonates, planned emergency research, or classified research is currently prohibited by the VA, while that involving prisoners requires prior written permission from the Office of Research Development (ORD). Research with pregnant women and/or their fetuses requires certification by the Medical Center Director (MCD) that the SFVAHCS has sufficient expertise in women's health to conduct the proposed research. The MCD must also approve international research not administered by the Collaborative Studies Program (CSP) and research involving children (under 18 years of age) that has been reviewed carefully by the IRB for its relevance to VA and is not greater than minimal risk.

aa. The **SFVAHCS Principal Investigator** has primary responsibility for the conduct of the research project at the SFVAHCS.

bb. A **serious adverse event (SAE)** is: 1) any untoward physical or psychological occurrence in a human subject participating in research that results in death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent or significant disability or

incapacity, congenital anomaly, birth defect, or 2) an occurrence when medical, surgical, behavioral, social, or other intervention is needed to prevent that outcome.

cc. **Serious unanticipated problems** include:

1) Interruptions of subject enrollments or other research activities due to concerns about the safety, rights, or welfare of human research subjects, research staff, or others.

2) Any work-related injury to personnel involved in human research, or any research-related injury to any other person, that requires more than minor medical intervention (i.e., basic first aid), requires extended surveillance of the affected individuals, or leads to serious complications or death.

3) Any VA National Pharmacy Benefits Management (PBM) Bulletins or Communications (sometimes referred to as PBM Safety Alerts) relevant to one or more of the VA facility's research projects.

4) Any data monitoring committee, data and safety monitoring board or data and safety monitoring committee report describing a safety problem.

5) Any sponsor analysis describing a safety problem for which action at the VA facility might be warranted.

6) Any unanticipated problem involving substantive harm, or a genuine risk of substantive harm, to the safety, rights, or welfare of human research subjects, research staff, or others.

7) Any problem reflecting a deficiency that substantively compromises the effectiveness of the VA facility's HRPP.

dd. A **systematic investigation** is an activity that
1) is planned in advance and
2) uses data collection and analysis to answer a question.

ee. **VA Research** is any research involving the use of VA resources.

ff. **VA Resources** are used when:

1) the research is sponsored by SFVAHCS; or

2) the research is conducted by or under the direction of any employee or agent of SFVAHCS in connection with his/her SFVAHCS responsibilities; or

3) the research is conducted on any property or within any facility of SFVAHCS; or

4) the research recruits veteran subjects on SFVAHCS property; or

5) the research involves the use of SFVAHCS's non-public information to identify or contact human research subjects or prospective subjects to use such data for research purposes.

4. **RESPONSIBILITIES:**

a. The **Institutional Official (IO)**

1) is ultimately responsible for SFVAHCS's research program, including implementation and oversight of the HRPP, and is assisted in this endeavor by the R&DC. Together, the IO and R&DC:

a) oversee all VA investigators and research staff,

b) develop and implement an educational plan for staff, investigators, and research staff including initial and continuing education, and

c) evaluate the HRPP at least annually.

2) must ensure that the IRBs function independently of facility leadership; to this end, IRB members have direct access to the IO if they have concerns about the functioning of the IRB or if they experience undue influence in their deliberations. The IO will promptly investigate allegations of undue influence; if the allegations are substantiated, the IO will remove the undue influence through any appropriate means.

3) is responsible for reporting serious unanticipated problems and unanticipated SAEs to the Office of Research Oversight (ORO) within five business days after notification by the IRB that such a determination has been made.

4) fulfills all educational requirements mandated by the VA Office of Research and Development (ORD) and OHRP;

5) ensures appropriate auditing of local human subjects research studies to assess compliance with all applicable local, VA, and

other federal requirements including, but not limited to, ORO requirements;

6) appoints one or more RCOs to conduct annual research consent document audits and triennial regulatory audits, and to assist in the VA facility's assessments of regulatory compliance;

7) reports any change in status of the RCO, such as a new appointment or resignation, to ORO Central Office, with a copy to the relevant ORO research officer, within 5 business days after the change takes effect;

8) provides a copy of any ORO compliance reports regarding the research program to the ACOS/R&D, any relevant research review committee(s), and the RCO in a timely fashion;

9) reports to ORO Central Office within five (5) business days:

a) any substantive memorandum of understanding changes (with a simultaneous copy to the appropriate ORO research officer)

b) any accreditation problems

10) delegates at least one person to interact with the VA Central IRB in the following roles:

a) provide comments or suggestions in response to the IRB's initial review considerations;

b) respond whether the SFVAHCS agrees or declines to participate in a particular study in response to the IRB's approval of the study PI application; and

c) serve as liaison between the SFVAHCS, the local site investigator, and the IRB;

b. The **Associate Chief of Staff for Research and Development (ACOS/R&D)** administers the Clinical Research Program with the assistance of the **Deputy Associate Chief of Staff for Clinical Research (D-ACOS/CR)**. The ACOS/R&D ensures that patent and royalty applications are reviewed and approved by ORD's Technology Transfer Office before they are initiated. Upon notification of a PBM Safety Alert from the Chief of Staff, the ACOS/R&D will forward the Alert to the Research Regulatory Coordinator.

c. The **CRO** coordinates the HRPP and maintains copies of all regulated

research proposals involving human subjects approved at the SFVAHCS. When advising researchers about the conduct of VA research, the CRO will incorporate applicable state and local laws governing human research; if there is a conflict between authorities, the CRO will consult with Regional Counsel and/or the Office of the General Counsel (OGC) Specialty Team Advising Research (STAR) attorney to resolve the conflict.

d. The **R&DC** provides the oversight of the HRPP to ensure regulatory compliance. The R&DC, at its discretion, seeks additional review, applies other contingencies to the approval of research, or stops any research previously approved, but does not have the authority to overturn a decision by one of its subcommittees or workgroups. The R&DC serves as the committee of record for initial review of exempt human subjects research, and delegates the continuing review of such research to the Subcommittee on Research Safety (SRS).

e. The **CRW** of the R&DC provides the expertise to review clinical research, including continuing review of previously approved research. Workgroup members are expected to demonstrate integrity and professional judgment at all times and must recuse themselves when there is a conflict of interest. The chair of the CRW or designee has authority to clear conditions placed by this workgroup and has signatory authority for VA and other interagency documents to document approval of human subjects research.

f. The **VA Central IRB (VA CIRB)** has the responsibility for reviewing protocols from the VA's Cooperative Studies Program (CSP) and other VA-specific multicenter studies.

g. The **UCSF CHR** serves as the SFVAHCS's IRB of record, reviewing all regulated human subjects research proposals that are not reviewed by the VA CIRB, and as the SFVAHCS's Privacy Board. As such, the UCSF CHR has been delegated the authority to:

1) approve, require modifications to secure approval, and disapprove all regulated human subjects research activities overseen and conducted by the SFVAHCS,

2) suspend or terminate IRB approval of research not being conducted in accordance with the IRB's requirements or that had been associated with unexpected serious harm to subjects, and

3) observe, or have a third party observe, the consent process

and the conduct of research.

The UCSF CHR has agreed to comply with VA requirements in reviewing VA research. When reviewing international research, the UCSF CHR will ensure that it has the appropriate expertise and knowledge of the locale through IRB members or consultants.

UCSF's CHR also has an active role in the SF VAMC Quality Improvement (QI) program through the auspices of their Quality Improvement Unit (QIU), which handles any participant or whistleblower complaints received by the CHR for any of the facilities for which it acts as IRB of record. QIU also processes post-approval events (e.g., reports of adverse events, non-compliance, and other research-related incidents), applying VA definitions and requirements where needed.

h. **Each IRB** reviews studies before research can begin, conducts continuing review of previously approved research, and has the authority to require cessation of research activities after approval. The provision of services by the IRB is established through a memorandum of understanding or other written agreement that outlines the responsibilities of the SFVAHCS and the IRB. VA officials may not approve research that has not been approved by one of SFVAHCS's IRBs of record.

IRB review of VA research includes, as necessary, verification that the manufacture and formulation of investigational or unlicensed drugs or devices conforms to federal regulations. The IRB is responsible for confirming that such drugs or devices have the appropriate legal and regulatory approval (e.g., IND, IDE) or meet the exemptions for such approval, and confirms that the IND or IDE number is valid.

Each IRB works very closely with the CRO and provides timely reports and documentation to meet the requirements of the SFVAHCS HRPP and applicable VHA Handbooks. The IRBs will promptly notify the CRO should they identify issues that require reporting to ORO, OHRP and/or FDA.

i. The **UCSF Conflict of Interest Advisory Committee (COIAC)** assists the CHR and the SFVAHCS's HRPP by reviewing any conflict of interest that may arise in human subjects' protocols reviewed by UCSF's CHR for SFVAHCS Principal Investigators who hold dual appointments as UCSF faculty.

j. The **RCO** performs routine audits of ongoing research and committee

processes. In particular, the Human RCO's primary responsibility is auditing and reviewing research protocols relative to requirements for the protection of human subjects. To fulfill this responsibility, the Human RCO conducts annual consent document audits and triennial regulatory audits on all regulated research protocols. The RCO serves as a consultant to any review committee or workgroup (e.g., R&DC, CHR, CRW) that so desires to provide additional expertise in compliance with applicable regulations and VA policies. The RCO reports directly to the MCD, and the RCO's activities may not be determined or managed by the Research Service, PIs, or any other research personnel.

k. The **Research Regulatory Coordinator** (RRC) has day-to-day responsibility for the conduct of research within the HRPP, and is responsible for monitoring changes in applicable policy and regulations, drafting policies, directing QI activities, filing required reports with regulatory authorities, assisting with regulatory visits by outside auditors, and forwarding PBM Safety Alerts to the Research Pharmacist. The RRC serves as the principal liaison with UCSF's CHR and may serve as the initial responder to, and site liaison with, the VA CIRB. The RRC has no budget or fiscal control beyond recommendations for CRO budgets and implementation of fiscal activities approved by the CRW and the ACOS/R&D.

The RRC also serves as the point of contact for subjects with questions about their rights as a research subject or complaints about research at the SFVAHCS. The RRC will answer questions within the RRC's area of expertise or refer the subject elsewhere as appropriate. Complaints will be investigated and if appropriate, discussed with the CRW, the D-ACOS/CR, and/or the ACOS/R&D, and/or referred to the RCO, Regional Counsel, and/or the MCD.

l. The **HRPP Coordinator(s) and Assistant(s)** are the CRO analysts with primary screening, record keeping, reporting, communication, and documentation responsibilities. The HRPP Coordinators and Assistants do not have independent authority to approve research or clear conditions established by review committees unless they have extensive experience (e.g., 5 years or more) in human research protection and/or demonstrate in-depth expertise in the subject matter (e.g., holding current certification in human research administration or compliance, such as Certified IRB Professional (CIP) or Certified in Healthcare Research Compliance (CHRC)), at the discretion of the DRO and the D-ACOS/CR, and have been specifically granted authority to review and clear nonmedical

conditions raised by the CRW. They may also serve as liaisons to the VA CIRB.

m. The **ISO** and the **PO** serve as *ex officio* (non-voting) members of the R&DC to ensure compliance with VA policies on data security and privacy, respectively.

n. The **Research Pharmacist** sits as a member of the CRW as a consultant in the handling of research pharmaceuticals, manages the research pharmacy, and controls all investigational drugs. Upon being notified of a PBM Safety Alert, the Research Pharmacist will (1) notify the RRC if the research pharmacy has supplies of the investigational drug in question, and (2) notify any investigators who have prescribing privileges for that drug, if applicable.

o. The **Chief Pharmacist** is responsible for oversight and control of investigational drugs, ensures appropriate pharmacy polices are current and that any requests for data extraction from Pharmacy Service or access to national dispensary databases for research purposes are cleared with the RRC or a designated member of the CRW.

p. The **Service Chiefs** are responsible for oversight and control of investigational devices used within their service, ensuring appropriate service level polices are current, devices are stored in a manner to prevent unauthorized use, and any request for use of investigational devices has current IRB and R&D approval. A Service Chief's signature on the Request for R&D Committee Approval form indicates the chief's agreement to provide special handling of devices where required.

q. The Office of **Regional Counsel** and **OGC STAR attorney** provide the legal support and interpretation of regulations, policy and guidance as needed to support all facets of the SFVAHCS HRPP. In particular, counsel reviews contracts, CRADAS, MOUs and other agreements prior to execution.

r. **NCIRE** administers grants from non-VA sponsors and ensures that all such applications receive the necessary review and approval (e.g., DOD IRB approval for DOD-funded projects). NCIRE monitors specific research training requirements for each sponsor and ensures that the VA CITI modules contain the necessary elements.

s. **The Principal Investigator** (PI) is responsible at all times for the

conduct of the research as approved and must ensure that research is conducted in compliance with all applicable policies and regulatory requirements, including procedures for attaining and maintaining the status of a SFVAHCS PI. If the research involves an investigational device, the PI is responsible for ensuring that the device is used only on an approved research protocol and that the prescribing physician is listed on that protocol.

t. **Investigators and research staff** must disclose to the applicable IRB any potential, actual, or perceived conflict of interest of a financial, professional, or personal nature that may affect any aspect of the research. They must also comply with all applicable VA and other federal requirements regarding conflict of interest.

u. **All members of the research community** are required to ensure that all apparent serious or continuing non-compliance and unanticipated problems in research involving risks to subjects or others are reported promptly to the applicable IRB. Apparent serious or continuing non-compliance, serious unanticipated problems involving risks to subjects or others, and local unanticipated SAEs must be reported to the IRB within five business days of initial notification; these reports are required in addition to other applicable reporting requirements (e.g., to the sponsor under FDA requirements).

5. **PROCEDURES:**

a. The SFVAHCS HRPP oversees all regulated research involving human subjects conducted on station or at any affiliated sites by SFVAHCS researchers while on official VA duty time. Individuals wishing to conduct such research are required to submit their application to the SFVAHCS's CRO for review and approval prior to undertaking or continuing any research activities.

National VA regulations and guidance concerning human subjects research are available publicly at http://www.research.va.gov/resources/policies/default.cfm. SFVAHCS HRPP policies and procedures are published on the VA intranet (only available within the VA secure network). UCSF CHR guidance is available at http://www.research.ucsf.edu/chr/index.asp and VA Central IRB guidance is available at http://www.research.va.gov/vacentralirb/default.cfm.

b. **Not Subject to HRPP Oversight:** Activities that do not constitute human subjects research (such as operations activities, program evaluation, quality improvement, case reports, and surveillance activities) do not require oversight by the SFVAHCS HRPP.

If a researcher is unsure whether the planned activity constitutes human subjects research under this policy, the researcher should consult the IRB or the SFVAHCS CRO. If a formal written determination is desired (e.g., as required by VHA Handbook 1058.05 paragraph 7.c if the activities will be published in a peer-reviewed journal), the researcher may:

1) submit an online application if the IRB of record is UCSF (if the activity does not constitute human subjects research as defined above, the IRB will respond with a "Denial of Review" letter), OR

2) submit a request to the authority for issuing such a determination (contact the SFVAHCS CRO for more information).

In addition, activities that have been granted a Humanitarian Device Exemption (HDE) by the IRB do not require SFVAHCS HRPP oversight.

c. **Recruitment-Only Approvals:** Recruitment materials for non-VA research can be posted and distributed with approval by a CRW member (or designee) and must include a disclaimer that the research is not sponsored or endorsed by VA and is provided for information only. The research must be relevant to Veterans and the mission of VA. Once an investigator obtains approval documentation from the CRW member or designee, the investigator must contact the Public Affairs office to request permission for posting.

d. **Requests for Exempt Certification:** Researchers are not permitted to make exempt determinations independently. All requests for exempt certification are subject to confirmation by the IRB, transfer to the R&DC as the initial committee of record, and continuing review by the SRS on an annual basis.

e. **Initial Review:** All initial applications are subject to review and approval by the R&DC. Applications for exempt research will be presented to the R&DC by a member with human subjects research expertise, preferably the CRW Chair, and reviewed and voted on by the full membership.

Applications for expedited or full committee human subjects research will be reviewed by the CRW for scientific merit if not otherwise peer-reviewed, by the ISO for adherence to station data security policies, by the PO for adherence to station privacy policies, and by the IRB for the protection of human subjects. Specific permission from the MCD or ORD, if required, will be sought after the study has received full approval from the IRB and the R&DC. Results of the scientific review will be communicated to the SFVAHCS PI by CRO staff. The PI will notify the IRB of these results through submission of a protocol modification, if necessary.

Final approval to conduct human subjects research cannot be released until the ACOS/R&D has received documentation of any necessary approvals from other subcommittees or workgroups (e.g., biosafety subcommittee, radiation safety subcommittee, UCSF COIAC) that have obligations to review and approve various facets of the proposed research.

f. **Continuing Review:** Investigators must maintain approval of all appropriate committees, subcommittees, and workgroups for the duration of the study. Ongoing compliance is monitored through the continuing review process and failure to maintain appropriate approvals may lead to delay or suspension of previously approved research.

Approval for non-exempt research involving human subjects is limited to a maximum of one year. Researchers are required to file a renewal application in a timely manner to avoid any lapse in study approval. Each renewal will undergo evaluation of the conduct of the research to date. All applications for renewal are reviewed by the IRB and may require additional review by other subcommittees or workgroups (e.g., biosafety, radiation safety). Applications that (1) indicate no changes in the approved VA research have occurred since the last renewal or (2) are requesting approval of a protocol for which the only ongoing VA procedure is data analysis will be reviewed administratively and reported to the CRW, while applications that include substantive changes in the VA portion of the study will require CRW review and approval.

If IRB renewal has been issued, but CRW approval has not, investigators may continue research activities with enrolled subjects, but may not enroll any additional subjects. When all approvals have been obtained, all research activities may resume.

g. **Informed consent forms** that are approved by the IRB are also considered approved by SFVAHCS once initial R&DC approval of the associated project has been granted, even in situations where the continuing review has not yet been approved by the CRW.

h. **Modifications:** All modifications must be submitted and approved by the IRB in writing prior to implementation. Minor (e.g., administrative, personnel) modifications will not be explicitly approved by the CRW. Major modifications (i.e., those that may affect the level of risk to subjects) involving activities at the SFVAHCS do require CRW review (including scientific review for DOD projects) and approval prior to implementation. Major modifications that do not involve activities constituting human research by the SFVAHCS require only administrative review at the VA.

i. **Adverse Events, Unanticipated Problems, Non-Compliance, and Suspensions or Terminations of Research by Outside Agencies** will be reported by researchers through the CRO following the guidelines for the appropriate IRB (CHR's guidelines may be found on their website). All reports will be reviewed by the RRC or an HRPP Coordinator or Assistant and the appropriate IRB, and may be forwarded to the CRW for discussion and/or action.

The IO is responsible for reporting a research problem or event to the appropriate authorities in the required manner within the time interval(s) specified. The problem or event may include serious and continuing non-compliance, unanticipated problems involving risks to subjects or others, and suspensions and terminations of research. The appropriate authorities Include VA's ORO for all research problems or events, ORD for unanticipated problems involving risks to subjects or others on VA-funded studies, VA Central Office for unanticipated adverse events involving risks to subjects or others, the VA Privacy Office for unanticipated problems involving the unauthorized use, loss, or disclosure of individually identifiable patient information, and/or the VHA Information Security Officer for unanticipated problems involving violations of VA information security requirements. The time interval specified is most commonly five business days after being notified. The IO's written report is required regardless of whether disposition of the event has been resolved at the time of the report.

The RRC is responsible for notification to the IO, internal committees, and other necessary parties (e.g., the Research Pharmacist for PBM Safety Alerts). Where permitted by the appropriate authority, the RRC is

responsible for filing follow-up reports (e.g., detailing any additional findings and appropriate remedial actions to the relevant ORO office at intervals and in a manner specified by that office).

The HRPP Coordinator or Assistant is responsible for communicating the outcome of the reviews to the researchers.

Where remedial actions involving a specific study or research team are required, the PI is responsible for ensuring that the actions are completed within 90-120 days after the IRB's determination. Where remedial actions involving programmatic non-compliance are required, the ACOS/R&D is responsible for ensuring that the actions are completed within 120-180 days after the IRB's determination, unless remediation requires substantial renovation, fiscal expenditure, hiring, or legal negotiations.

j. **Conflicts of Interest:** After ORD notifies the ACOS/R&D of approval of patents and royalties, the ACOS/R&D will notify the IRB and R&DC through the CRO of a VA protocol with a potential institutional financial interest. The ACOS/R&D will also refer the PI to the Office of Regional Counsel or OGC STAR attorney, who will evaluate whether an institutional financial conflict of interest exists and consult with the appropriate committee, subcommittee, or workgroup for management strategies. The IRB has the final authority to grant IRB-approval of the research associated with the patent and royalties through its review of initial, continuing or modifications to the related research.

PIs disclose potential financial conflicts of interest by completing the applicable section of the study application to the IRB. UCSF COIAC manages such conflicts for applications reviewed by UCSF CHR, while the CRW manages such conflicts for applications reviewed by the VA Central IRB. Since each management committee has a "no conflicts allowed" policy, approval is withheld until identified conflicts are eliminated. Management of potential conflicts is reported to R&DC through the minutes of each IRB or a separate workgroup report, as applicable.

k. **Cyber-Security and Data Incident Reporting:** Research staff must abide by the station's ISO and PO policies for data security and privacy protection, and incidents implicating these policies must follow the procedures described therein. See Research Policy 151-26 for additional information.

l. **Education and Credentials:** The SFVAHCS requires all

investigators, research staff, and other personnel participating in, or reviewing, human subjects research to commit to an ongoing program of research education; the mandatory training module on the HRPP required of all patient care personnel is not a substitute for the required research training.

Investigators, research staff, CRW members, VA representatives to the IRB, R&DC members subject to this requirement, and HRPP staff must complete the appropriate VA CITI training modules at least every three calendar years. Initial training for researchers must be complete before engaging in human subjects research, while initial training for other personnel must be complete within 30 days of becoming subject to the requirement.

Completion of CITI training is automatically tracked by the provider and verified by SFVAHCS administrators. Researchers whose training is not current will be notified by SFVAHCS HRPP personnel; they will not be permitted to perform human subjects research, and their access to SFVAHCS computer systems may be suspended.

Research staff without clinical privileges, or whose privileges do not sufficiently encompass their research duties, are required to maintain a valid scope of practice document which outlines the tasks delegated to them by each SFVAHCS-approved PI for whom they work; nothing in this policy shall permit an individual to work outside of their credentials and/or privileging. Scopes do not expire, but PIs will review the scopes of practice for all associated research staff during the annual review of a particular project and will submit a revised scope as needed.

m. **HRPP Resources:** Resources (including, but not limited to, space, personnel, continuing education opportunities, and access to Regional Counsel) available to the HRPP are evaluated annually by the R&DC during its review of the program, continually by the D-ACOS/CR during regularly scheduled strategic planning and operational meetings of the CRO, and as needed by the ACOS/R&D in response to requests by the RRC or D-ACOS/CR.

The budget for the HRPP is submitted annually to medical center management through the CRW and the R&DC as part of the overall research budget. NCIRE augments the HRPP budget through salary and general fiscal support.

n. **International Research**

1) International research is subject to the same policies, procedures, and processes as domestic research, including those for initial review, continuing review, review of modifications to previously approved research, and post-approval monitoring (including handling of complaints, non-compliance, and unanticipated problems involving risk to subjects or others).

2) For CSP studies, PIs must obtain a waiver from the Chief Research and Development Officer (CRADO) prior to conducting international research as defined in this policy. Current requirements for obtaining a waiver can be found on the VA website. The PI must submit the required materials to the CRO for review by the ACOS/R&D. Following review by the ACOS/R&D, the CRO will request review and approval by the MCD on the PI's behalf, and will then forward the application to the CRADO.

The application for a waiver must demonstrate:

a) Knowledge of local laws, regulations, customs, and practices, and agreement to follow the same

b) Knowledge of, and adjustment for, cultural context, including translating study documents into the local language, as appropriate

c) Investigators and research staff are qualified to conduct research in the locale

d) Adequate coordination and communication with local IRBs or Ethics Committees, when appropriate

e) That all international sites hold international federalwide assurances and the research is approved by the listed IRB or Ethics Committee

3) The PI must conduct the research in accordance with VA requirements and all other applicable federal requirements for protecting human subjects, tissue banking, use of databases, federal criminal laws, and the standards of ethical conduct for employees of the federal branch.

o. **Quality Improvement Plan**

1) The HRPP assesses its performance through

a) annual reports to its accrediting body, ORO, and the

R&DC

b) the results of the annual informed consent and triennial regulatory audits by the RCO

c) metrics on HRPP processes (e.g., the volume of applications processed, the time interval between receipt of applications and final approval by the ACOS/R&D)

d) periodic audits by ORO

2) The HRPP endeavors to reduce the rate (per hundred protocols) of reportable findings on the RCO audits while maintaining high customer satisfaction (quantified by number of serious complaints received by leadership annually). A reportable findings rate of 5% or higher, or a complaint rate of 1 per month annually, would indicate that the HRPP has not met its goal.

6. **REFERENCES:** 38 CFR 16; 21 CFR 50, 56, 312, 361, and 812; 18 USC 201; 5 CFR 2635; VHA Handbook 1058.01; VHA Handbook 1058.05; VHA Handbook 1200.01; VHA Handbook 1200.05; VHA Handbook 6500; VHA Directive 2005-050; VA IT Directive 06-2; Federalwide Assurance (FWA) FWA00000280; MCM 119-08, Research Policy 151-26. VA/AFGE Master Agreement Articles 53 and 63.

7. **RESCISSIONS:** MCM 11-19 dated 28 February 2013.

8. **INITIAL EFFECTIVE DATE:** Unknown.

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