

**HUMAN SUBJECT PROTECTION AGREEMENT
BETWEEN
U.S. DEPT. OF VETERANS AFFAIRS PALO ALTO HEALTH CARE SYSTEM,
PALO ALTO VETERANS INSTITUTE FOR RESEARCH AND
THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY**

Introduction/Preamble

This agreement describes the relationship between Veterans Affairs Palo Alto Health Care System (VAPAHCs), the Palo Alto Veterans Institute for Research (PAVIR) and The Board of Trustees of the Leland Stanford Junior University (Stanford) in assuring the protection of human subjects in VAPAHCs research, including the responsibilities of each, in utilizing Stanford's Institutional Review Boards (IRBs).

This agreement is entered into by and between the U.S. Department of Veterans Affairs Palo Alto Health Care System (VAPAHCs), with its principal office and place of business at 3801 Miranda Avenue, Palo Alto, CA; Palo Alto Veterans Institute for Research (PAVIR), which includes as legally inseparable its officials and employees with its principal office and place of business at 3801 Miranda Avenue, Palo Alto, CA; and Stanford, which includes as legally inseparable entities its officials and employees with its principal office and place of business at Stanford, CA, 94305.

WHEREAS, VAPAHCs and PAVIR wish to retain, pursuant to the terms and conditions of this agreement, the services of Stanford through its Vice Provost and Dean of Research and its IRBs, i.e., Medical Administrative Panels on Human Subjects in Research to perform research review functions as required by statute and regulations of DHHS and DVA; and

WHEREAS, Stanford and VAPAHCs are interested in facilitating collaborative VA Research by Stanford faculty members and VA clinicians and research investigators, both institutions recognize the administrative preference of Stanford hosting IRB review of VA Research and wish to avoid the inefficiencies of duplication of efforts in IRB review; and

WHEREAS, all parties to this agreement agree that the Veterans Health Administration (VHA) Central Office operates a VHA Central Office Institutional Review Board (VA CIRB) and that the VA CIRB will have oversight and jurisdiction for the initial and continuing review as well as review of amendments, monitoring, reporting, and other relevant requirements, for select Veterans Health Administration multi-site research projects involving human subjects as set forth in a separate Memorandum of Understanding (MOU) between VHA Central Office and VAPAHCs. Stanford IRB will have no oversight or jurisdictional responsibility for VA CIRB research.

WHEREAS, all parties to this agreement understand that the ethical conduct of research is a shared responsibility requiring cooperation, collaboration, and trust among institutions, investigators and their research staff, the subjects who enroll in research, and the Institutional Review Boards' members and staff; and

WHEREAS, Stanford's IRBs possess valuable skills, knowledge, expertise, and resources in the area of human subject protection in research; and

WHEREAS, Stanford, VAPAHCS and PAVIR recognize the presence of common professional and community standards; familiarity with each other's operational policies, constraints, procedures, and commitments; and geographic proximity of the institutions;

Therefore, in consideration of the promises and undertakings set forth herein, VAPAHCS, PAVIR, and Stanford agree as follows:

A. Applicability

Except for human subjects research submitted to the VHA Central Office IRB by VAPAHCS, this agreement applies to all human subjects research conducted or supported by VAPAHCS until this MOU be amended.

The VA facility Director is the individual legally authorized as Signatory Official to commit VAPAHCS to an Assurance. The Director serves as the official representative of the Institution to external agencies and oversight bodies, and provides all written communication with external departments, agencies, and oversight bodies.

The term "VA research" includes VA investigators (serving on compensated, WOC, or IPA appointments) involved in VA research while on VA time in space leased to or used by VA. The research may be funded by VA, by other sponsors, or be unfunded. All VA research is federally conducted and supported; therefore, all federal and VA requirements apply.

VAPAHCS and Stanford acknowledge that the Stanford Federalwide Assurance indicates that Stanford follows the Belmont Report rather than the Common Rule for certain nonfederal human research. Stanford agrees to apply 38 CFR 16 (The Common Rule); 45 CFR 46 and Subparts; and VHA Handbook 1200.05 to all VA conducted or supported research, as well as other pertinent VA and federal requirements.

PAVIR is a nonprofit corporation authorized under Title 38, subchapter IV and established under 38 USC §7361-7366 to provide a flexible funding mechanism for the conduct of research approved by the VAPAHCS Research and Development Committee. PAVIR has no authority to approve or conduct research independently. PAVIR complies with requirements for a written agreement with the IRB of Record in 45 CFR §46.114 and 38 CFR §16.114. PAVIR, VAPAHCS and Stanford wish to avoid duplication of effort in the oversight of cooperatively conducted human studies research. PAVIR research is VA-approved research subject to policies and procedures contained in VA Directives, Handbooks, regulations and statutes, PAVIR, VAPAHCS and Stanford agree that all oversight for such studies will be provided by VAMC and the University IRB

B. Institutional Responsibilities

1. Stanford and VAPAHCS, agree that they are collectively responsible for attempting to identify research proposals prior to their initiation that meet the definition of VA Research, in order that such research may be processed and reviewed in accordance with this MOU.

2. Stanford, VAPAHCS and PAVIR will maintain their respective Federalwide Assurances (FWAs) with the Department of Health and Human Services' Office of Human Research Protections and agree to abide by the terms of these FWAs. Each will notify the others of any changes in the status of the FWA. Stanford acknowledges that VAPAHCS may not collaborate with institutions that do not have an FWA or an Assurance acceptable to the VHA Office of Research Oversight (ORO).
3. Stanford authorizes the designation of the Stanford Health and Human Services registered IRBs for review of research under the VAPAHCS FWA00000929 and PAVIR FWA00000937.
4. Each institution will support and maintain open channels of communication across institutional boundaries between IRB members and staff, investigators and research staff, facility management, research administrators and institution officials regarding human subject protections.
5. Stanford, VAPAHCS and PAVIR will comply fully with the requirements set forth at 38 CFR 16, 38 CFR 17 research provisions; as well as 45 CFR 46, 21 CFR 50 and 56, (where applicable) and VHA Handbook 1200.05 for review and oversight and conduct of research involving human subjects. VAPAHCS will adhere to VA requirements and to University requirements to the extent permitted by federal policy.
6. VAPAHCS agrees to provide the Stanford IRBs access to all relevant investigator records (including data files, regulatory files/binders, case report forms, sponsor queries, internal and external monitoring reports, and audit reports); research subjects' clinical and research records or case files; and facility research records (including sponsor agreements), as required for oversight and monitoring of research activity. This access will be provided to any individual(s) designated by the IRB.
7. Stanford agrees to provide the VA facility and the VHA Office of Research Oversight ORO with access for review and copying any IRB or other records, documents, or reports relevant to compliance reviews of research conducted or supported by VA, approved by the VA facility's R&D Committee, or involving individuals with VA appointments; provide VA R&D Committee copies of IRB Meeting minutes for the VA related protocols; provide access to, or information from, the IRB database (if any) to approved representatives of the VA for the purposes of tracking ongoing VA research activity.
8. Stanford and PAVIR acknowledge that the VAPAHCS R&D Committee represents a required second level of review for all VA Research. No VA Research may be undertaken without VA R&D Committee review and approval. When funding for VA Research will be administered by Stanford or PAVIR, Stanford and PAVIR will notify the protocol director that authorization by the VAPAHCS R&D Committee is necessary prior to expenditure of funds or accrual of subjects in VA Research.
9. VAPAHCS and its R&D Committee cannot approve research that has been disapproved by a Stanford IRB. If, in the course of its review, the R&D

Committee requires changes to the protocol that relate to the determination of the protection of human subjects, the R&D Committee must refer those changes to the IRB for its approval before the R&D Committee can give final approval.

10. VAPAHCS remains ultimately responsible for the maintenance of its overall institutional system to protect human subjects.

11. VAPAHCS will periodically assess Stanford IRB performance as to VA Research in the following essential components of the VAPAHCS Human Research Protection Program:

- a. Content and accuracy of informed consent forms; VAPAHCS will provide VA-specific language for informed consent documents.
- b. IRB analysis of risks and benefits including designation of minimal risk;
- c. Special considerations and protections for vulnerable or potentially vulnerable populations;
- d. Privacy and confidentiality protections;
- e. Continuing review of approved research;
- f. Ongoing review of previously approved research ,e.g., review of amendments and reportable events;
- g. Use of expedited review or other procedures requiring review of less than the full IRB;
- h. Granting exemption from Federal requirements for IRB oversight ;
- i. Granting waivers for documentation of informed consent;
- j. Granting waivers of any elements of informed consent;
- k. Managing Stanford conflict of interest requirements for IRB members

This will be accomplished via:

- a. Regular review of IRB documents pertaining to VA Research by the VAPAHCS R&D Committee;
 - b. Annual review of IRB composition by VAPAHCS for regulatory compliance, appropriate expertise for the research being reviewed, and inclusion of representatives with an interest in or experience with vulnerable populations;
 - c. Annual review of documented IRB policies and procedures for compliance with applicable regulations;
Regular meetings and/or communications between VAPAHCS Research Administration staff and IRB administrative staff.
12. As part of VAPAHCS annual review of HRPP resources and resource requirements required by VHA Handbook 1200.01, the R&D Committee will review the VA HRPP, including the IRB, annually. . This report will summarize the functioning of the IRBs with respect to VA Research and delineate any problems, realized or potential, therewith. An analysis of the volume of research considered by the IRBs will be included in the report. This report will be discussed at an R&D Committee meeting where Stanford's Research Compliance Director and a VA representative to the IRB are invited to attend.

13. VAPAHCS will ensure via written communication with Stanford's Research Compliance Office that the IRBs are informed of all federal and VA requirements relating to the protection of human subjects in research.
14. Each institution will develop and maintain mutually acceptable policies for monitoring human subject research and for regular communication of results of this monitoring, and other documentation of human subjects research.
15. Stanford and its IRBs will incorporate in or attach to their IRB Standard Operating Procedures any policies and procedures specific to VA Research. VAPAHCS will cooperate in maintaining currency of the SOPs with respect to changes in VA requirements.
16. VAPAHCS, Stanford and PAVIR will collaborate to maintain a system of protections applicable to all human subject research covered by this agreement.
17. Each institution remains responsible for safeguarding the rights and welfare of human subjects within its local context.
18. Each institution will require disclosure of conflict of interest by individuals conducting research, i.e. individuals designing research, directing research, serving as principal investigator, enrolling subjects, making decisions regarding subject eligibility to participate in research, analyzing or reporting research data, or submitting manuscripts concerning the research for publication. All disclosed conflicts will be managed, mitigated, or eliminated by Stanford or VAPAHCS.

19. Stanford and VAPAHCS are responsible for educating the members of their research community in order to maintain a culture of compliance with Federal regulations and institutional policies relevant to the protection of human subjects. Training may be conducted jointly. Each institution will track required training for completion.

Each institution will maintain specific mechanisms, consistent with VHA Handbook 1058.02 and other applicable VA and federal requirements, to address allegations of research misconduct involving VA human subject research or VA employees involved in human research. Allegations of research misconduct involving VA employees and/or VA research will be monitored by ORO.

20. VAPAHCS is responsible for implementation, within VAPAHCS local research context, of appropriate oversight mechanisms to ensure compliance with the determinations of the reviewing IRB.
21. VAPAHCS and Stanford acknowledge the understanding that each party shall be responsible and liable for the negligent conduct of its own research and any and all resulting damages or injury to human subjects.
22. Stanford acknowledges that the privacy provisions of the federal law – the Health Insurance Portability and Accountability Act of 1996 (HIPAA) – apply to

health information created or maintained by health care providers who engage in certain electronic transactions, that the Department of Health and Human Services (DHHS) has issued the regulation entitled "Standards for Privacy of Individually Identifiable Health Information" applicable to entities covered by HIPAA, and that the services provided under this Agreement may involve the receipt and use of Protected Health Information (PHI) as defined in 45 CFR 164.501. Furthermore:

(a) Stanford may use PHI to conduct IRB review and oversight activities on behalf of VAPAHCS as specified throughout this Agreement, provided that such use would not violate the Privacy Act, Title 5 U.S.C. 552a, if done by VAPAHCS. Use and disclosure of VA PHI pursuant to this Agreement is limited to the use and disclosure of PHI by the IRB under its regulatory authority for oversight. Use and disclosure of PHI will be described in research protocols, data use agreements, separate contracts or Cooperative Research and Development Agreements (CRADAS) as required by VHA Handbook 1200.05. Stanford agrees to report to VAPAHCS any use or disclosure of the Protected Health Information not provided for by this Agreement in accordance with VHA Handbook 1058.01

(b) Stanford agrees to use appropriate safeguards to prevent use or disclosure of the Protected Health Information other than as provided for by this Agreement.

(c) Stanford agrees to document disclosures of Protected Health Information and information related to such disclosures as would be required for a covered entity to respond to a request by an individual for an accounting of disclosures of Protected Health Information in accordance with 45 CFR 164.528.

23. Stanford IRB(s) shall review requests for Waivers of Authorization for VA Research for approval and will review HIPAA authorizations as required by VHA Handbook 1200.05. As applicable, VAPAHCS will provide required VA language for the Authorizations. VAPAHCS will obtain protocol review by the facility Privacy Officer and Information Security Officer. The Privacy Officer will assure all requirements have been met prior to the initiation of the research.
24. The Stanford IRB shall report to VAPAHCS per the requirements of VHA Handbook 1605.1 and VA Handbook 6500 when any incident of unauthorized use, loss, or disclosure of individually-identifiable VAPAHCS study subject information occurs. Stanford IRB is responsible for implementing written policies and procedures that comply with the data security reporting policies of VAPAHCS that will enable them to report within the timeframes established by VA in Handbook 1058.01
25. Per VA Handbook 6500.2, The Stanford IRB agrees to establish written procedures for notification of the VAPAHCS Information Security Officer and VA R&DC within one hour of becoming aware of any violations of VA information security requirements of which it becomes aware.

26. As required by federal and VA requirements, VAPAHCS shall promptly inform the appropriate federal agency (e.g., OHRP, FDA, NIH, etc.) of:
 - (a) any unanticipated injuries or problems involving risks to subjects or others in VA Research;
 - (b) any serious or continuing noncompliance with the provisions of this agreement or the determinations of the IRB; and
 - (c) any suspension or termination of IRB approval for VA Research protocols.

VAPAHCS will copy Stanford's Research Compliance Director, and Stanford's Vice Provost and Dean of Research on all letters to Federal agencies provided under this Section.

27. VAPAHCS monitoring reviews of research protocols are considered to be part of the HRPP monitoring activities. Consequently, Stanford may rely on VAPAHCS monitoring reviews for purposes of satisfying its monitoring requirements.

C. Institutional Review Board Responsibilities

28. Stanford IRBs assume responsibility for initial and continuing review and continuing oversight of all protocols submitted to them as VA Research. The IRBs will have the authority to approve, require modification in, or disapprove all VA Research involving human subjects. The IRBs will have the authority to suspend or terminate approval of VA human subject research. The IRBs will have the authority to observe and/or monitor VA Research to whatever extent necessary to protect human subjects.
29. In reviewing VA protocols, the IRBs will comply fully with the requirements of all applicable Federal and VA policies and guidelines.
30. IRB reviews of activities identified as VA Research will take into account the required criteria for approval, the facilities and capabilities of VAPAHCS, the measures taken by VAPAHCS to ensure compliance with their determinations, as well as the VAPAHCS community attitudes.
31. The membership of each IRB panel will include at least two voting members who are VAPAHCS representatives. VAPAHCS shall assist the IRBs in recruiting VAPAHCS representatives for IRB membership. The VAPAHCS Director will appoint the VA IRB members and alternates in writing. The IRB will provide current IRB rosters to VAPAHCS within 25 days of a change of membership to permit VAPAHCS to report to ORO as required by VHA Handbook 1058.03.
32. The IRBs will maintain processes to identify the financial conflict of interest of individuals reviewing and conducting research as it relates to human subject protection.

33. The IRBs may require that the proposed research is reviewed and approved by VAPAHCS or Stanford committees on Radiation Safety, Bio-Safety, or other relevant VA or Stanford committees prior to granting their own approval.
34. The membership of each IRB will include at least one member who does not have any association with Stanford, VAPAHCS or PAVIR and is not part of the immediate family of a person who is affiliated with these organizations.
35. Provide training to VA staff and investigators as appropriate for them to comply with affiliate IRB policies and submission procedures as they apply to VA submissions.
36. The IRBs will prepare and maintain adequate documentation of activities in accordance with applicable regulations.
37. The IRBs shall maintain records to document the current IRB approval status of the VA's current research. Such records will be made accessible to authorized VAPAHCS personnel and others with legitimate rights of access.
38. IRB records will be maintained and/or stored as required to protect the privacy and confidentiality of subjects.
39. The IRBs will retain records for a minimum of six years following completion of the study. Should VAPAHCS be required to maintain records for a longer period of time as part of the federal records schedule, arrangement will be made for transfer or copying of such records.
40. The IRBs will inform the VAPAHCS R&D Committee in writing of all identified VA Research that was reviewed and the outcomes of each of these reviews after each IRB meeting.
41. The IRBs will make records related to VA Research accessible for inspection and copying by authorized representatives of VA, including accreditors and appropriate Federal departments or agencies, at reasonable times and in a reasonable manner.
42. The IRBs will report the following (a-e) promptly to Stanford and VAPAHCS officials within a timeframe that will enable VAPAHCS to report as required by VHA Handbook 1058.01, as well as to any applicable regulatory authority. VAPAHCS will report the following to the IRB when encountered during the conduct of VA research:
 - a. any unanticipated injuries or problems involving risks to subjects or others in VA Research;
 - b. serious adverse events (whether anticipated or unanticipated, whether related or unrelated to the research)
 - c. any serious or continuing noncompliance with the provisions of this agreement or the determinations of the IRB; and
 - d. any suspension or termination of IRB approval for VA Research protocols;
 - e. Any unresolved complaints from subjects or others.

43. The IRBs will provide the VA R&D Committee copies of any reports or correspondence related to VA Research to or from regulatory and compliance enforcement agencies or offices, including PHS, NIH, OHRP, and FDA, upon their receipt or dispatch.
44. Stanford's IRBs may be called into an interim review session by the Chairperson at the request of any IRB member or appropriate Stanford or VAPAHCS official to consider any matter concerned with the rights and welfare of any subject involved in VA Research.

D. Principal Investigator Responsibilities

1. Stanford, VAPAHCS, and PAVIR acknowledge that Principal Investigators are responsible for ensuring the following:
 - a. All VA human subject research covered by this agreement has received initial prospective review and approval by a Stanford IRB;
 - b. continuing review and approval of the research has been accomplished within the time frame stipulated by the IRB;
 - c. the research is conducted at all times in compliance with all applicable regulatory requirements and the determinations of the designated IRB;
 - d. VA R&D Committee approval has been received prior to any VA Research activity commencing;
 - e. no changes in approved research protocols or consent forms are initiated without prior IRB approval, except where necessary to eliminate apparent immediate hazards to subjects;
 - f. no research may be continued beyond the IRB-designated approval period;
 - g. any serious adverse events or unanticipated problems involving risks to subjects or others are promptly reported to the IRB and VA Research Administration per the requirements of VHA Handbook 1058.01;
 - h. any serious or continuing non-compliance with applicable regulatory requirements or determinations of the designated IRB of which investigators become aware are promptly reported to the IRB and VA Research Administration per the requirements of VHA Handbook 1058.01;
 - i. copies of any reports or correspondence to or from any regulatory or compliance enforcement agency, such as OHRP, FDA, etc, that exercises oversight for the protection of human subjects in research are provided to the IRB.

E. Performance Period

1. This agreement shall be effective upon March 18, 2016 and shall remain in effect for a period of three years.

F. Financial Remuneration

1. Sponsored VA research administered by PAVIR is subject to initial and continuing review IRB review fees. Request for payment of these fees will be directed to PAVIR.

PAVIR agrees to pay appropriate charges within 30 days of receipt of invoice referencing specific protocols for which review has been completed.

G. Termination

1. This MOU may be amended at any time as conditions change. Amendments will be signed by all parties to this agreement.
2. Either party may terminate this agreement if the other party breaches any of its obligations or provisions, or by mutual agreement for any reason, provided however, that the parties shall receive not less than ninety (90) days prior written notice of such intent to terminate and the opportunity to cure any default during such period.
3. The process for termination of this agreement by either the VA facility or Stanford will be in an orderly manner so as not to harm subjects or put subjects at risk. Stanford agrees that IRB oversight of VA research and this agreement will not be terminated until all the research is transferred to the oversight of another IRB or safely closed.
4. VAPAHCS and PAVIR agree that if this agreement should be terminated they shall amend their FWAs to remove Stanford as designated IRB of Record. If reasonably possible, the effective date of the amendments of the FWAs shall be the effective date of the termination.

H. Notices/Modifications

Any changes or modifications should be mailed to:

Stanford

Contact Title: Research Compliance Director
Name: Kathy McClelland
Address: Administrative Panels Office
Stanford University, Stanford, CA 94305

VAPAHCS

Contact Title: ACOS/Research and Development

Name: Philip Tsao, Ph.D.
Address: VA Palo Alto Health Care System
3801 Miranda Avenue (151), Palo Alto, CA, 94304-1290

PAVIR

Contact Title: Chief Executive Officer
Name: Kerstin Lynam
Address: P.O. Box V-38
Palo Alto, CA, 94304-0038

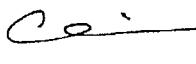
I. Applicable Law

1. This Agreement shall be construed, interpreted and enforced under federal law and, when not inconsistent, the laws of the State of California.

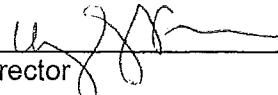
J. Signature Page

IN WITNESS WHEREOF, the parties hereto have executed this agreement as of the date set forth above.

THE BOARD OF TRUSTEES OF THE LELAND STANFORD JUNIOR UNIVERSITY:
By: Ann M. Arvin, M.D.

Signature: 
Title: Vice Provost and Dean of Research

VETERANS AFFAIRS PALO ALTO HEALTH CARE SYSTEM:
By: Elizabeth J. Freeman

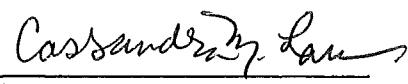
Signature: 
Title: Director

PALO ALTO VETERANS INSTITUTE FOR RESEARCH:
By: Kerstin Lynam

Signature: 
Title: Chief Executive Officer

Date: 03/21/2016

VETERANS INTEGRATED SERVICE NETWORK:
By:  Sheila M. Cullen

Signature: 
Title: Director