

The Stanford University Human Research Protection Program (HRPP) Policy Manual is the primary source document for the IRB policies and procedures. It serves as a reference and guide for investigators, IRBs, administrators, and other members of the research community.



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Ch. 1: The Human Protection Program (HRPP)

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

The Stanford University Research Policy Handbook [Human Research Protection Program](#) provides information about the organization, scope, authority and responsibilities associated with the Stanford University HRPP for the research community at Stanford University and its affiliates, and explains how the HRPP has been incorporated into one core document.

1.1 Organizations Covered by the HRPP

The five Stanford affiliated organizations are:

- Stanford University
- Stanford Hospital and Clinics (SHC)
- Lucile Packard Children's Hospital at Stanford (LPCH)
- Veterans Affairs Palo Alto Health Care System (VAPAHCS)
- Palo Alto Veterans Institute for Research (PAVIR).

Any components of these organizations as listed in their [Federalwide Assurances](#) (FWAs) are considered part of that organization for purposes of the HRPP and are covered by this HRPP Policy Manual.

SHC and LPCH are California non-profit corporations whose sole member is the Board of Trustees of Stanford University. They provide hospital, clinic, and physician services in affiliation with the Stanford University School of Medicine. [SHC](#) and [LPCH](#) each maintain an MOU with Stanford University that retains and requires Stanford University to carry out the HRPP on their behalf. This document also requires that they agree to cooperate with Stanford University and take all necessary actions to allow Stanford University to carry out the HRPP. Both SHC and LPCH file a [FWA](#) appointing the Stanford University IRBs to review their human subject research.

VAPAHCS is operated by the US Department of Veterans Affairs to provide hospital, clinic, and physician services in the region of Palo Alto and Stanford, California. It is affiliated with Stanford University and its School of Medicine. Many of its physicians and investigators are also faculty at the School of Medicine who conduct research at VAPAHCS facilities. PAVIR is a non-profit corporation established and controlled by VAPAHCS pursuant to 38 USC 7361 and 7368. Its purpose is to provide a flexible funding mechanism for the conduct of approved research (i.e., externally sponsored research) at VAPAHCS facilities and through VAPAHCS physicians and investigators. Both VAPAHCS and PAVIR file a [FWA](#) appointing the Stanford University IRBs to review their human subjects research. VAPAHCS and PAVIR also maintain a

[memorandum of understanding](#) with Stanford University relating to the HRPP. This document is similar to the agreement with SHC and LPCH but provides that VAPAHCS “remains ultimately responsible for the maintenance of its overall institutional system to protect human subjects.” This occurs through the VAPAHCS Research and Development Committee. Additionally, the memorandum of understanding between VAPAHCS and Stanford University formally establishes the Stanford University IRBs as the Research Privacy Board for VAPAHCS and PAVIR.

1.2 Goal and Objectives of the HRPP

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

The goal of the HRPP is to protect human research participants by ensuring that in all Stanford research:

- The rights and welfare of human research participants are adequately protected.
- Such research is guided by the ethical principles of respect for persons, beneficence, and justice as set forth in the Belmont Report, and is conducted with the highest level of expertise and integrity.
- Such research complies with applicable laws.

Objectives of the HRPP

The HRPP includes mechanisms to:

- Establish a formal process to monitor, evaluate, and continually improve the protection of human research participants and dedicate resources sufficient to do so
- Exercise oversight of research protection
- Educate investigators and research staff about their ethical responsibility to protect research participants
- When appropriate, intervene in research and respond directly to concerns of research participants.

Written Plan for the HRPP

The written plan for the HRPP is comprised of policies, guidance, and supporting documents governing human subject research and the protection of participants. The HRPP is approved by the Vice Provost and Dean of Research. All documentation comprising the HRPP is available on the [Human Subjects Website](#).

1.3 Delegation of Responsibility for Stanford University HRPP Implementation

Stanford delegates responsibility for the Human Research Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program. (AAHRPP Element I.1.B)

For the organizations covered by the HRPP, the President of Stanford University delegates the primary responsibility to the Vice Provost and Dean of Research to establish, maintain, and oversee the HRPP. (See [Delegation of Authority to Institutional Officer](#) and [Research Policy Handbook](#)).

Stanford considers the HRPP Policy Manual to be a dynamic document because the scientific developments, ethical issues, and regulatory circumstances that shape it are continuously evolving and improving. The Research Compliance Office (RCO) maintains policies and written procedures reflecting the current practices of the IRB in conducting reviews and approvals of human research. As part of the RCO Continuous Quality Improvement (CQI) program, the RCO Director, in consultation with CQI and senior HRPP staff, regularly reviews (i.e., at least annually) and refines the HRPP Policy Manual and written procedures and makes recommendations for modifications or develops new policies and procedures as appropriate. The Vice Provost and Dean of Research may approve a modification of any portion of the HRPP Policy Manual. The RCO Director may approve modifications to the HRPP Policy Manual that relate to the day-to-day review and operational functions of the IRB; other modifications of the HRPP Policy Manual must be approved by the Vice Provost and Dean of Research.

The RCO is responsible for disseminating all modifications to the HRPP Policy Manual and incorporating them into the relevant educational programs (discussed in [Chapter 4](#)).

1.4 Research Covered by the HRPP

Stanford has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program. (AAHRPP Element I.1.A)

Types of Human Subjects Research at Stanford

Stanford conducts or oversees biomedical, social science and behavioral research. Human subject research is covered as stated in the [Federalwide Assurance](#) – for Stanford. Stanford University has chosen to limit the scope of its Federalwide Assurance (FWA) to federally funded research.

Human Subjects Research in which Stanford is Engaged:

- It is considered “human subject research” - as defined in any one of the following:
 - FDA regulations
 - DHHS regulations or other Common Rule regulations

- VA regulations ([VHA Directive 1200.05 and 1200.21](#)- Classified research involving human participants cannot be approved by the Stanford IRB), or
- Any other applicable state or local regulations, e.g., California State regulations

and

- Stanford (or its employees or agents) is engaged in the research – as defined by being involved in one or more of the following activities (in accordance with the OHRP guidance Engagement of Institutions in Human Subjects Research):
 - Receiving an award through a grant, contract, or cooperative agreement directly from HHS or other federal agency for the non-exempt human subjects research (even when all human research activities are conducted by non-Stanford personnel);
 - Sponsoring or overseeing a human subjects research study regardless of funding or location (even when all human research activities are conducted by non-Stanford personnel);
 - Intervening for research purposes with any human subjects of the research by performing invasive or noninvasive procedures;
 - Intervening for research purposes with any human subject of the research by manipulating the environment;
 - Interacting for research purposes with any human subject of the research;
 - Obtaining the informed consent of human subjects for the research.
 - **Obtaining** for research purposes identifiable private information or identifiable biological specimens **from any source** for the research.

Agents include all individuals performing institutionally designated activities or exercising institutionally delegated authority or responsibility, including students, faculty, staff, employees, visiting scholars.

See [Chapter 3.3](#) for HRPP Policy Manual policies and procedures for determining when studies meet the regulatory definitions of human subject research.

Actions Required before Stanford Will Allow an Investigator to Assume the Role of Sponsor or Manufacturer

Manufacturing an investigational product for testing in humans or sponsoring a clinical trial (including designing a clinical trial), whether foreign or domestic, may cause Stanford to assume significant legal, regulatory, and financial obligations, and may engage Stanford in research, even when a third party will serve as the investigator or manufacture the investigational products on behalf of Stanford.

- Investigators (including faculty who plan to hire third-party investigators) must consult the IRB before undertaking any activity (including sub-contracting with a third party to make the investigational product) that will place Stanford in the role of the manufacturer of an investigational product intended for use in humans.
- Investigators (including faculty who plan to hire third-party investigators) must consult the IRB before undertaking any activity or requesting any agreement that would cause Stanford to assume the obligations of a clinical trial sponsor.
- In each case, the IRB will determine whether local IRB review is required and will alert the investigator to other potentially applicable requirements, including FDA manufacturing and export regulations, FDA IND or IDE submission, institutional contract review, and insurance.

Approvals Required Before Human Subject Research Commences

IRB approval is required before research activities may commence.

In addition to approval from the IRB, depending on the funding source, either contract finalization or departmental approval is required before research involving human participants can commence, as follows:

- ***Externally funded research (industry-sponsored clinical trials and other clinical research)*** undergoes a parallel review process by a combination of the following, depending on the funding source:
 - *For the School of Medicine:* Research Management Group ([RMG](#)) develops and negotiates budget and payment schedules, routes/ensures approvals, negotiates terms and conditions, signs contracts, issues notices of award (NOA) for industry-sponsored clinical trials
 - *For other Schools:* Office of Sponsored Research ([OSR](#)) negotiates terms and conditions, signs contracts, issues notices of award (NOA) for industry-sponsored clinical trials
 - *For all Schools:* Industrial Contracts Office ([ICO](#)) handles Industry Research Agreements and Material Transfer Agreements (MTAs)
 - *For VA research:* The VA Research and Development Committee must approve all VA research
- **Other research** (see [Chapter 1.7](#)) requires approval by a Division Chief, Department Chair, School Dean or designee, or Academic Sponsor as appropriate, confirming:
 - Scientific and scholarly validity
 - Adequacy of resources.

Some protocol-specific situations require additional review and approval by other organizational components or must meet their standards (see [Chapter 2.4](#)).

1.4.1 International Research

Stanford international (transnational) research activities are consistent with the ethical principles set forth in its Human Research Protection Program and meet equivalent levels of participant protection as research conducted in the Stanford principal location while complying with local laws and taking into account cultural context. (AAHRPP Standard I-3)

Researchers should ensure that participants outside the US have the equivalent protections that participants would be afforded in the US. OHRP provides a compilation of regulations and guidelines that govern human subjects research in other countries, as well as standards from a number of international and regional organizations.

See:

- OHRP [International Compilation of Human Subject Protections](#)
- For VA research: [VHA Directive 1200.05](#) and [1200.21](#) for definitions and requirements for international research.

The IRB has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance. (AAHRPP Element II.4.A as of 2011)

Permission must be obtained from the local Medical Center Director, prior to initiating any VA-approved international research. All international research must also be approved explicitly in a document signed by the VA medical facility Director, except for Cooperative Studies Program activities which must be approved by the CRADO. The local Medical Center Director will not grant permission for an international research study involving prisoners as research subjects.

Researcher Responsibilities

When studies are conducted in other countries (i.e., outside the US) researchers should be knowledgeable about the local laws and customs which apply to the research, and the cultural context in which they will be working. They should ensure that participants in international research are afforded equivalent protections to those participating in the US and must describe their qualifications and preparation for the research that enable them to estimate and minimize risks to subjects. Researchers are asked to consider these issues on the International Research form, [APP-11](#).

IRB Responsibilities

Stanford IRB review of international research adheres to the same policies applied to domestic (US) research, when appropriate. Additional legal or cultural expertise may be consulted by the IRB during its review, and the IRB will make those determinations required by the laws of the

countries in which the research is conducted. The IRB will also request documentation of local IRB or local research/ethics committee review, when appropriate.

Considerations for Informed Consent

The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (AAHRPP Element II.3.F)

In some circumstances it may be inappropriate to document consent by using the standard written and signed consent document, and there might be different rules on determining e.g., who may serve as a legally authorized representative (LAR). Refer to [Chapter 12](#) for information on waivers and alteration of consent, etc.

Additional Requirements

For federally funded research, the regulations of that sponsoring agency apply, and the required federal protections must be provided; it is not sufficient to provide “equivalent” protections.

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for other requirements depending on the source of support/funding (e.g., Department of Defense, Department of the Navy).

1.5 Primary Officials, Administrative Units, and Individuals of the HRPP

Stanford delegates responsibility for the Human Research Protection Program to an official with sufficient standing, authority, and independence to ensure implementation and maintenance of the program. (AAHRPP Element I.1.B)

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

Officials Responsible for the HRPP

The primary responsibility for the HRPP lies with Stanford University through the Vice Provost and Dean of Research. See RPH [Human Research Protection Program](#). The President of Stanford University delegates this responsibility to the Vice Provost and Dean of Research. The Board of Trustees of Stanford University, the governing body of Stanford University (as established by Jane and Leland Stanford in the 1885 Founding Grant), appoints the President.

Dean of Research Office responsibilities and organization are described in Administrative Guide [Chapter 9](#).

As Stanford University's Institutional Official, the Vice Provost and Dean of Research signs the Federalwide Assurance of Compliance (FWA) on behalf of the institution's HRPP and is ultimately responsible for:

- Creating, establishing, and maintaining the policies and procedures for the HRPP and related research policies and procedures on behalf of Stanford University
- Overseeing the protection of human participants, regulatory compliance, and the implementation of the HRPP for Stanford
- Ensuring that open channels of communication are maintained between the components of the HRPP
- Overseeing research investigators and staff, and research management
- Ensuring the independence of the IRB, including the authority to act without undue influence
- Requiring periodic reviews of the HRPP
- Ensuring that the HRPP is functional, adequately staffed and funded, involving:
 - i) Annual review of the resources allocated to the HRPP
 - ii) Participation in the annual budget preparation for the HRPP and incorporation of the HRPP budget into the budget of Stanford University.

The day-to-day operational and oversight responsibility for the HRPP is delegated to the Research Compliance Office (RCO) Director, a non-faculty, full-time administrator. The RCO Director reports to the Vice Provost and Dean of Research.

The [Research Compliance Office \(RCO\)](#) Director has day-to-day operational responsibility for the HRPP through the RCO. Among other functions, the RCO Director is administratively responsible for the operations of the IRBs, the Institutional Animal Care and Use Committee (IACUC), the IRB/SCRO (IRB and Stem Cell Research Oversight) Panel, and in conjunction with Environmental Health and Safety, assists the Biosafety and Radiological Safety Committees.

VAPAHCS Research and Development Committee: This committee is ultimately responsible for all human subject research which occurs at VAPAHCS. Its membership, functions and responsibilities are described in the VAPAHCS Health Care System Memorandum No. 151-15-11, Research and Development Committee and Associated Subcommittees.

IRBs

The Administrative Panels on Human Subjects in Medical Research and the Administrative Panel on Human Subjects in Non-Medical Research are the Institutional Review Boards (IRBs) and perform many of the core functions of the HRPP. The Vice Provost and Dean of Research appoints the chairs and the members of the IRBs and assigns their authority and responsibility in the “charge” to the Chairs and members. See Charge to the [Administrative Panel on Human Subjects in Medical Research](#) - IRB by the Vice Provost and Dean of Research, [Charge to the Administrative Panel on Human Subjects in Medical Research – IRB/SCRO](#) by the Vice Provost and Dean of Research, and Charge to the [Administrative Panel on Human Subjects in Non-Medical Research](#) by the Vice Provost and Dean of Research. The charge emphasizes that the IRBs are functionally independent (e.g., of the individuals who are conducting the research) and have ready access to the highest officials of the covered organizations, if needed, to ensure protection for human research participants.

There are seven medical IRBs and one nonmedical IRB. Their authority, membership requirements, and responsibilities are described in [Chapter 6](#). IRBs are responsible for the initial and continuing review, review of modifications, approval of all research subject to the HRPP, determining serious or continuing noncompliance, requiring modification (to secure approval), disapproving research, and applying applicable ethical standards.

Stanford ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Stanford conducts or oversees. (AAHRPP Standard I-2)

HRPP Staff in the Research Compliance Office (RCO): The HRPP Associate Director is responsible for supporting the daily operations of the IRBs and the education program. The IRB staff review protocol applications for accuracy and completeness and act as liaisons between the Protocol Directors (PDs) and the IRB members. Senior IRB staff are responsible for the training of all individuals who are affected by the Human Research Protection Program. The

Continuous Quality Improvement (CQI) program is an integrated part of the Research Compliance Office and ensures periodic evaluation and strengthening of the HRPP.

Upon request, the RCO has responsibility for review and comment on proposed external regulations dealing with human research. When appropriate, the RCO formulates and recommends draft policies and procedures for approval by the appropriate Stanford University bodies and promulgation by the Vice Provost and Dean of Research.

Researchers

Principal Investigator/Protocol Director: The Stanford individual ultimately responsible for a protocol is the Protocol Director (PD). Most (but not all PDs) have faculty appointments at Stanford University. PD responsibilities are specified in the HRPP Policy Manual and include ensuring that:

- All Stanford human subject research has received initial prospective review and approval by the IRB.
- Continuing review and approval of the research has been accomplished within the time frame stipulated by the IRB.
- The research is conducted at all times in compliance with all applicable regulatory requirements and the determinations of the IRB.

Other Members of the Research Team: Every member of the research team is responsible for protecting human participants. Investigators, study coordinators, research nurses, research assistants, Academic Sponsors, student/staff investigators, and all other research staff have the following strict obligations to:

- Comply with all IRB determinations and procedures
- Adhere rigorously to all protocol requirements
- Inform the PD, and thus IRB, of unanticipated problems
- Ensure the adequacy of the informed consent process
- Take necessary measures to ensure adequate protection for study participants.

See [Chapter 14](#) and [Chapter 15](#) for more on responsibilities and duties under the HRPP.

Sponsored Research

Sponsors can be a company, institution, individual donor, or organization responsible for the initiation, management, or financing of a research study. Both the sponsor and Stanford have obligations to protect research participants.

Participant Outreach

Participants in a research project also have responsibilities. These include telling the truth, asking for clarification, following the protocol, notifying study personnel of their non-compliance, and telling investigators if they wish to withdraw from the study.

HRPP Organizational Components

In addition to the Vice Provost and Dean of Research and the RCO, human research protection responsibilities are shared by these Stanford University [HRPP](#) components:

The Stanford Cancer Institute (SCI) draws upon the expertise of more than 300 researchers and clinicians from the Schools of Medicine, Engineering and Humanities & Sciences to advance research discoveries and medical innovation and provide comprehensive patient care. Within SCI, the Cancer **Clinical Trials Office (CCTO)**: provides administrative, research, and educational services to Cancer Center investigators conducting clinical trials. Programs serve to increase awareness and accrual to clinical trials as well as to improve the quality and efficiencies of conducting clinical trials in compliance with regulatory, documentation, and oversight requirements. Its goals are to:

- Facilitate clinical trials and translational research by providing administrative support to all Cancer Center investigators
- Enhance and facilitate data collection and reporting of clinical cancer research
- Provide programs to contribute to quality assurance and the ongoing education of Cancer Center Clinical Research Personnel
- Coordinate outreach efforts in the community to increase clinical trials awareness and accrual, and
- Promote interdisciplinary collaborations and translational medical research.

All cancer-related studies are reviewed by the CCTO Scientific Review Committee ([SRC](#)), (except observational studies, retrospective chart reviews, compassionate use studies, and multiple program projects (MPPs)). The Data Safety Monitoring Committee of the CCTO reviews adverse event reports and requires them, as appropriate, to be submitted to the IRB. (See [Chapter 3.10](#)).

Institutional Conflict of Interest Committee (ICOIC): The ICOIC of the School of Medicine (SOM) reviews COI disclosures from all protocols (SOM and non-SOM) submitted to the IRB. The ICOIC considers the conflicting interests, determines or assesses any mitigation or management plan,

and determines whether the conflict can be managed or needs to be eliminated. If further review is appropriate, the case is examined by the Vice Provost and Dean of Research. The decisions and actions of the ICOIC are reported to the IRB staff and considered by an experienced IRB member or at an IRB convened meeting. See [Chapter 3.7](#) for more information.

Environmental Health and Safety (EH&S) ([EH&S](#)): EH&S provides and coordinates programs and services that minimize risks to safety and health, and environmental and regulatory risks to the Stanford University community in a manner consistent with responsible fiscal and environmental stewardship. EH&S works with investigators to promote safe and healthful laboratory environments that support the University's science and research mission. The [Administrative Panel on Biosafety \(APB\)](#) and Health Physics [Radiation Safety](#) are under the auspices of EH&S. As appropriate:

- Human subject research must have APB approval before research activities may commence;
- The [Protocol Application](#) contains questions about radioisotopes and radiation machines; the Radiation Safety Committee must certify that it has reviewed a protocol using radioisotopes or radiation machines and recommends it for approval. Without this approval, a study which employs these modalities cannot be approved by the IRB, and must either be approved contingent upon receiving Radiation Safety Committee approval, or tabled to a future convened meeting;
- The Protocol Application instructs that patient related equipment, if used, must meet standards established by the Hospital Instrumentation and Electrical Safety Committee.

Clinical and Translational Research Unit (CTRU) ([CTRU](#)): The CTRU was formerly the General Clinical Research Center (GCRC). The CTRU is an NIH-funded core facility for the [Stanford University School of Medicine](#). CTRU facilities and services include:

- Clinical space (outpatient)
- Research nursing support
- Clinical sample laboratory processing and specialized assays
- Bionutrition research support
- Mentorship of junior investigators

It supports studies (including cancer studies) that are conducted in the main hospital, the Veterans Affairs Palo Alto Health Care System, and Lucile Packard Children's Hospital.

Stanford Affiliated Covered Entity (SACE) ([SACE](#)): SACE includes Stanford Hospital and Clinics, Lucile Packard Children's Hospital, and the Stanford University HIPAA Components.

- Privacy Governance Council: The Privacy Governance Council is convened by the Stanford University Privacy Officer to explore issues related to the implementation

and enforcement of the Privacy and Security rules under HIPAA for the Stanford Affiliated Covered Entity.

Internal Audit and Institutional Compliance: Audit liaisons work with the various entities to carry out audit activities. In addition, the Institutional Compliance Program is carried out by a number of [compliance offices](#), with oversight residing under the Associate Vice President for Internal Audit and Institutional Compliance.

Office of the General Counsel (OGC): The OGC is responsible for addressing all of the legal issues arising out of the activities of Stanford University, Stanford Hospital and Clinics and Lucile Salter Packard Children's Hospital at Stanford. A representative of the OGC serves as an ex-officio IRB member and is available for consultation on issues regarding human subject research and participant protection.

Leadership for research administration at Stanford University is jointly shared between the Office of the Vice Provost and Dean of Research and the Office of Business Affairs. The Office of Sponsored Research ([OSR](#)) manages pre- and post-award research services for the university, including negotiation of sponsored agreements, award set-up and closeout. OSR works in close collaboration with a number of partner groups in other central and school offices to help ensure the overall effective coordination of research administration services, systems, policies, and processes. OSR prepares, negotiates and oversees federally-funded contracts, sub-awards and subcontracts. Effective October 2011, contract administration for industry-sponsored clinical trials has been consolidated within the School of Medicine Research Management Group ([RMG](#)).

The Research Administration Policy and Compliance Office ([RAPC](#)) oversees Cost & Management Analysis (CMA), Property Management, Accounts Receivable, Service Centers and Space Management.

Office of Technology Licensing (OTL): OTL is responsible for managing the intellectual property assets of Stanford University. The OTL charter is to help turn scientific progress into tangible products, while returning income to the inventor and to the University to support further research. OTL has signature authority on behalf of the University for license agreements, material transfer agreements, industrial contracts and other agreements that pertain to intellectual property*. Of particular relevance to human subject research protections are:

- Clinical Technology Assessment Agreements (CTAA's) - created when a sponsor provides an investigational drug or device for research; the protocol must have IRB approval, and, as appropriate an IND or IDE.
- Material Transfer Agreements (MTA's) - these govern the use of tangible research materials distributed to other institutions. The Protocol Application asks whether tissues are to be distributed as part of such an agreement.

* Except for clinical trial agreements, which are handled by the [Office of Sponsored Research \(OSR\)](#), the **Industrial Contracts Office (ICO)** within OTL is responsible for negotiating

and signing [sponsored research](#), [material transfers](#) (including Material Transfer Agreements with non-profits and government agencies) and related research agreements with industry.

Risk Assessment Committee (RAC): The Risk Assessment Committee is a high-level, multi-disciplinary group that evaluates human subject research protocols for financial or administrative risks, or when a request is made to waive a policy related to clinical trial operations and administration. The RAC is comprised of representatives from the School of Medicine, Hospital Financial Services, Hospital Compliance, Office of the General Counsel and University Risk Management. RAC provides an additional vehicle for risk analysis but does not evaluate human subject protections, conflict of interest, or scientific validity; RAC may have observations in these three areas but does not have any formal responsibility for action in such matters. RAC makes recommendations on whether or not to waive School of Medicine policy to the Senior Associate Dean for Research.

Research Management Group (RMG): For School of Medicine research - Provides oversight and management of sponsored projects and ensures compliance with sponsor and University expectations for managing sponsored funds. RMG performs a parallel review to the IRB, and confirms IRB approval before routing sponsored project information to the Office of Sponsored Research ([OSR](#)) contracts office. Effective October 2011, it also supports contract administration for industry-sponsored clinical trials (see above).

Stanford Center for Biomedical Ethics (SCBE): The SCBE is dedicated to interdisciplinary research and education in biomedical ethics and provides clinical and research ethics consultation. SCBE serves as a scholarly resource on emerging ethical issues raised by medicine and biomedical research and is called upon for consultation by the IRB when needed.

Stanford Center for Clinical and Translational Research and Education ([Spectrum](#)): Spectrum serves Stanford faculty and clinical research personnel in the School of Medicine (SOM), Stanford University Medical Center, Lucile Packard Children's Hospital (LPCH) and Veterans Affairs Palo Alto Health Care System (VAPAHCS). Its mission is to enhance the quality of clinical and translational research by:

- Aligning organizational “service” based activities
- Providing education, training, and mentoring to clinical research coordinators and staff
- Developing an integrated research infrastructure

IRB staff and Spectrum collaborate to provide education to the research community, disseminate information about the HRPP, and to facilitate quality improvement activities such as compliance reviews.

Stanford University [Schools](#): Although human subject research (including undergraduate research programs) takes place within any of the seven schools, most human subject research is performed by the Schools of Medicine, Education, and Humanities & Sciences, which includes

the Department of Psychology. All such research must receive IRB approval before research activities can commence.

1.6 Ethical and Legal Principles Governing Human Subject Research

Ethical Principles

The primary ethical principles applied to research covered by the HRPP, including protocols “exempt” under federal regulations pertaining to human subject research, are those set forth in The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research of the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (Belmont Report).

The three main principles are:

Respect for persons (e.g., applied by obtaining informed consent, considering privacy and confidentiality, and adding protections for vulnerable populations)

Beneficence (e.g., applied by weighing risks and benefits)

Justice (e.g., applied by the equitable selection of subjects)

All parties involved in the conduct of research are expected to also adhere to the principles of expertise (“competent to do the work”) and integrity (“faithfully adhere to professional principles”). Ethical principles from other sources (e.g., International Conference on Harmonization) may also be applied to research covered by the HRPP, for example:

- To an individual protocol because its particular circumstances raise a type of ethical issue that most other protocols do not
- When they are recognized by the federal or other funding source or the state or country where the research will occur
- When they have been developed for specific areas or types of subjects (e.g., embryos and fetal tissue, illiterate subjects).

Investigator training on the ethical principles governing human subject research and investigator responsibilities is provided by the tutorial [Principal Investigator Responsibilities at Stanford University](#). These principles are also covered in the [CITI tutorial](#) for investigators, IRB Members, and IRB Staff, and in the orientation given to new IRB members.

With respect to sponsored research, Stanford University and PAVIR address the protection of research participants by including in their standard contract templates a provision that the sponsor acknowledges and understands that the Stanford HRPP is applicable to all human participant research. See [Chapter 16](#).

Legal Principles

The basic legal principles governing human subject research, covered by the HRPP and applicable to individual protocols are:

- Federal Policy for Protection of Human Subjects (Common Rule) in 45 CFR Part 46
- Food and Drug Administration Regulations for the Protection of Human Subjects in 21 CFR Parts 50 and 56
- Standards for Privacy of Individually Identifiable Health Information (HIPAA Privacy Rule) in 45 CFR Parts 160 and 164.
- Department of Veterans Affairs regulations in 38 CFR Part 16 and [VHA Directive 1200.05](#)
- Applicable California law.

These and other legal principles are addressed when applicable in individual chapters of this manual.

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board or Ethics Committee, as appropriate. (AAHRPP Element I.1.D)

Additional Requirements

Depending on the source of support for research, regulations from other agencies such as DoD, DOJ, etc. might apply. See [Other Federal Agencies - Additional Requirements](#) [GUI-42].

1.7 Scientific and Scholarly Validity Review and Ethics Review

Stanford has and follows written policies and procedures for reviewing the scientific or scholarly validity of a proposed research study. Such procedures are coordinated with the ethics review process. (AAHRPP Element I.1.F)

Scientific and Scholarly Validity Review

When evaluating the scientific and scholarly validity of a protocol, the IRB relies on the review provided by different entities, as follows:

- For federally sponsored research, including VA-funded research, the peer review process by the sponsoring agency (e.g., NIH, NCI, DOD) provides scientific and scholarly review.
- For research subject to FDA review, the FDA conducts a rigorous scientific design review during IND or IDE evaluation. Most industry-sponsored research falls within

this category. An important exception is Non-Significant Risk (NSR) device research, where the IRB serves, in a sense, as the FDA's surrogate with respect to review and approval of NSR studies.

- For research occurring at the VA Palo Alto Health Care System (VAPAHCS), the VA Research and Development Committee (R&D) and subcommittees perform scientific review of all activities prior to initiation and at least annually thereafter, in order to evaluate the quality, design, desirability and feasibility of each new R&D proposal/application for funding, to assure maintenance of high scientific standards, protection of human research participants including privacy and confidentiality, and adequate safety measures. The process is described in VAPAHCS Memorandum No. 151-15-11, Research and Development Committee and Associated Subcommittees.
- The Cancer Center Scientific Review Committee (SRC) provides a peer review of local and national research protocols involving cancer patients treated at Stanford University Clinical Cancer Center and Lucile Packard Children's Hospital. The review primarily focuses on the scientific merit of the study and applies to all phases of clinical therapeutic intervention, behavioral clinical trials, tissue and body fluid research, and diagnostic trials, which impact medical decision making for the treatment of cancer patients. The process is described in the SRC [website](#). All cancer studies are required to undergo SRC review with the exception of prospective biospecimen studies that are not investigating a scientific hypothesis and compassionate use studies for a single patient.

For research that has departmental funding, gift funding or no funding, or that has not otherwise gone through a scientific review as described above, the IRB requires that:

- *In the School of Medicine:* the Division Chief or Department Chair of the PD's department, (or the School Dean or his designee when the Division Chief or Department Chair has a conflicting interest), or
- *In other schools:* the School Dean or designee

submit a [Review of Scientific and Scholarly Validity](#) [APP-10]) and confirm to the IRB that scientific review of the protocol has occurred. This submission is not necessary for retrospective charts reviews.

For **all** research conducted by students, including student research that may undergo scientific review by an awarding entity, this confirmation is provided by the Academic Sponsor who is responsible for the scientific review. The Academic Sponsor must submit a [Review of Scientific and Scholarly Validity, and Oversight](#) [APP-9] to the IRB.

The signatures on these documents confirm the soundness of the research design and the ability of the research to achieve its aims.

Stanford ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Stanford conducts or oversees. (AAHRPP Standard I-2)

Submission of [APP-10](#) is not required for minimal risk retrospective chart reviews. However, [APP-9](#) is still required for student chart reviews, since this form also confirms faculty oversight. For regular review protocols, the PD must answer the questions in the [Scientific Review Protocol for Human Subjects Research](#) [NOT-13].

For *all* research, the IRB evaluates, in accordance with federal research regulations [45 CFR 46.111(a) and 21 CFR 56.111(a)] whether the following requirements are satisfied:

Risks to participants (physical, psychological, social, legal, and economic) are minimized (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose participants to risk; and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

Risks to participants are reasonable in relation to anticipated benefits, if any, to participants, and the importance of the knowledge that may be expected to result.

If the requirements noted above are not satisfied, the protocol may not be approved as written. The IRB reviewer(s) may consider other scientific reviews, as noted above, (e.g., NIH peer review, SRC review) in their evaluation. For protocols where the protocol design is unusual or novel, in addition to the protocol being assigned to primary reviewer(s) with relevant expertise, input from ad hoc consultants may also be obtained. For further information, refer to guidance [Evaluating Sound Study Design](#) [GUI-17].

Ethics Review

The IRB review of the study procedures, risks and benefits includes the identification, evaluation and resolution of the ethics issues presented in the study in accordance with the ethical principles outlined in [Chapter 1.4](#). If necessary, the IRB may seek ad hoc assistance from ethical consultants, both internal and external (e.g., members of the hospital ethics committees of SHC, LPCH, or VAPAHCS, or members of Stanford University's Center for Biomedical Ethics).

An ethics review (in addition to the scientific review) is also conducted by the internal review committees for research done in the Clinical and Translational Research Unit ([CTRU](#)) at SHC and LPCH, and in the Cancer Center at SHC and LPCH.

An ethics review (in addition to the scientific review) is also conducted by the internal review committees for research done in the Cancer Center at SHC and LPCH.

Ethics consults are also available for researchers, via the Spectrum Biomedical Ethics program, with the Stanford Center for Biomedical Ethics (SCBE). Initial ethics consultations for study design, bedside or bench side consultations, are scheduled through the [Center for Integration of Research on Genetics and Ethics website](#)

Additional Requirements

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for other requirements depending on the source of support/funding (e.g., Department of Defense, Department of Justice).

Ch. 2: Resources Supporting the HRPP

2.1 Sufficient Human and Fiscal Resources

Stanford ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Stanford conducts or oversees. (AAHRPP Standard 1-2)

The provision of adequate human and fiscal resources facilitated through the budgeting process results in a well-functioning and effective HRPP.

Human Resources: Stanford University demonstrates a high level of institutional commitment to its HRPP in terms of human resources. The HRPP is led by the Vice Provost and Dean of Research, pursuant to the authority delegated by the Office of the President (see [Delegation of Authority to Institutional Officer](#)). The Vice Provost and Dean of Research oversees the Research Compliance Office (RCO).

Fiscal Resources: Stanford University demonstrates a high level of institutional commitment to its HRPP in terms of fiscal resources and is committed to providing the RCO with adequate means to carry out its mission while keeping the protocols-to-staff-ratio within acceptable boundaries.

Resource Allocation in support of HRPP: The RCO receives its annual budget through the Office of the Vice Provost and Dean of Research.

The annual budget is established by a three-phase process:

1. IRB Chairs provide input regarding priorities and resources needed for the new academic year. This input is included in the Annual Report and communicated to the Vice Provost and Dean of Research in a written report. Any questions from the Vice Provost and Dean of Research are communicated to the RCO Director to discuss with the IRB Chairs.
2. The RCO Deputy Director and budget officers in the Office of the Vice Provost and Dean of Research prepare income and expense forecasts for the following year. Income forecast includes fees collected for the review of protocols on company-sponsored clinical research. Expenditure forecast takes into consideration:
 - Adequate number of IRBs
 - Adequate staffing
 - Adequate technology support
 - Access to meeting space
 - Adequate funds for educational opportunities for IRB members and IRB staff, including off-site conferences

- Adequate funds to provide on-going office and logistic support
 - Adequate funds to carry out agreed-upon special projects.
3. These forecasts are converted into a budget ultimately reviewed and approved by the Provost. This budget is then integrated by the University Budget Office into the University's consolidated budget forecast presented to the Board of Trustees for approval. It takes effect on September 1 of each year.

During the fiscal year, the RCO Deputy Director and the budget officers in the Office of the Vice Provost and Dean of Research analyze and explain any variance between actual income and expense (or projected income and expense) and the Consolidated Budget of the RCO, in accordance with the guidelines provided by the University Budget Office (Administrative Guide Memo 3.1.2 - University Funds). When unanticipated needs arise, they are communicated by the RCO Director to the Vice Provost and Dean of Research. These needs are considered in light of their urgency and fiscal implications.

Other components of the HRPP have similar budget and review processes.

2.2 Matching IRBs to Volume and Types of Human Research

Stanford ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Stanford conducts or oversees. (AAHRPP Standard 1-2)

Each IRB meets at least once a month, with the exception of:

- The non-medical IRB (IRB 2), which does not meet in August or in months when no presented protocols are included on the agenda, and
- Those IRBs which process only expedited and exempt protocols and do not meet routinely.

The non-medical IRB reviews research conducted in the field of human behavior, social sciences, education, anthropology, and other similar areas. This IRB generally will not review protocols with physical interventions, e.g., MRI, venipuncture, or actions that involve the collection or analysis of protected health information.

Human subject research protocols which also involve stem cells are usually assigned to IRB/SCRO; those involving gene transfers are usually assigned to IRB 1.

The RCO assesses its level of activity at least annually in order to optimize the workflow and IRB load. It considers the ratio of protocols to staff, the number of transactions generated by each protocol, the type of protocols (regular, expedited or exempt), and any other appropriate elements. Input from the IRB Chairs regarding the level of activity and other IRB-related matters are gathered in the IRB annual report that is presented to the Vice Provost and Dean of

Research. When adjustments are necessary, their financial implications are considered during the budget process outlined above in [Chapter 2.1](#).

New IRBs or new staff positions are created to meet the demands of the workload. [Meeting schedules and corresponding protocol submission deadlines](#) are posted on the Human Subjects Research website. Submitted protocols are assessed for completeness before their assignment to an IRB. Once a protocol is assigned to an IRB, the review process can start. This includes a detailed pre-meeting review phase that ensures that substantive issues and compliance requirements are addressed in a timely fashion. See [Chapter 7](#) for information on the review process.

2.3 Human Research Protection, Care of Participants, and Safety

Stanford ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Stanford conducts or oversees. (AAHRPP Standard I-2)

The IRB has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society. (AAHRPP Element II.3.A)

To approve research, the IRB must determine that, where appropriate, there are adequate resources to ensure the care and safety of participants, from the screening and recruitment phases throughout the project (for VA projects, Stanford VA adheres to [VHA Directive 1200.05](#)). During review of the submitted protocol, the IRB assesses the information in the eProtocol Application and as necessary asks for additional details. (See [Chapter 7](#) for information about the review process.) If the protocol does not provide adequate protection, it will not be approved.

Protocol Directors (PDs) are required to indicate in the Protocol Application whether investigators: will have access to a population that will allow recruitment of the required number of participants; will have sufficient time to conduct and complete the research; will have adequate numbers of qualified staff; will have adequate facilities; will have a process to ensure that all persons assisting with the research are adequately informed about the protocol and their research related duties and functions; and will have medical or psychological resources available that participants might require as a consequence of the research when applicable.

When the protocol is not funded by a contract or a grant, the availability of resources is affirmed by the Academic Sponsor, the Division Chief, Department Chair, School Dean or their designee (as appropriate to the sponsorship/funding and administration of the study).

PDs should continually monitor the resources allocated for their research and notify the IRB if any change in the availability of resources may adversely impact the rights and welfare of participants.

2.4 Communication and Interaction

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

Communication

The IRB ensures that the communications required by the information supplied in the eProtocol Application take place. The Intake Checklist and the Protocol Checklist are used when reviewing a protocol application to ensure that situations which require communication and interaction between various components of the HRPP are handled appropriately:

- **The Radiation Safety Committee** must certify that it has reviewed a protocol using radioisotopes or radiation machines and recommends it for approval. Without this approval, a study which employs these modalities will either be tabled to a future convened meeting or will be approved contingent on Radiation Safety Committee recommendation for approval. If a modification involves review by Radiation Safety, the IRB will hold its approval until Radiation Safety forwards its approval to the IRB. Radiation Safety is given access to the protocol information by the IRB.
- **Protocols involving biosafety materials** and requiring review by the Biosafety Panel must be reviewed by this Panel and receive an approval letter in addition to review by the IRB. A new protocol generally will not be presented at an IRB convened meeting until the Biosafety Panel has approved it. If a modification or continuing review involves review by Biosafety, the IRB will hold its approval until Biosafety forwards its approval to the IRB. The HRPP Associate Director and the IRB Manager are ex-officio members of the Biosafety Panel. A member of the IRB staff attends the Biosafety Panel meetings and receives communications directly from the Panel regarding submitted protocols. The Biosafety Officer and Biosafety Specialist (from the Environmental Health & Safety department) are ex officio members of the medical IRBs and IRB/SCRO and attend medical IRB and IRB/SCRO Panel meetings.
- **Protocols that also involve the use of human stem cells, human embryos, or their derivatives** must be reviewed and approved by the IRB/SCRO (IRB/Stem Cell Research Oversight) Panel, in addition to having an IRB protocol reviewed and approved by IRB/SCRO, prior to activity commencement.

- ***Patient related equipment using electricity*** must meet the standards established by the Hospital Instrumentation and Electrical Safety Committee. For protocols using such equipment, the investigator is referred to Clinical Engineering.
- ***Investigator Conflict of Interest disclosures:*** All investigator conflicting interest is managed via the Conflict of Interest Review Program (COIRP) and its associated Institutional Conflict of Interest Committee (ICOIC). The IRB will not approve a protocol until any disclosed COI has been reviewed and resolved by the COIRP/ICOIC, and as appropriate, a plan or strategy to adequately eliminate, mitigate, or manage the conflict has been determined by the COIRP/ICOIC. See [Chapters 3.7](#), [6.3](#), and [14.1](#).
- ***An FDA investigational drug or biologic that is not under the control of the hospital pharmacy (SHC or LPCH):*** The PD must have a Security and Controlled Access Plan for the drug or biologic on file with the applicable pharmacy. See [Chapter 5.2](#).
- ***Blood, tissue, or data (slides, X-rays, etc.) that are being transferred in or out of the institution, and there is no contract in place:*** The PD must coordinate with the Office of Technology Licensing (OTL) about a Material Transfer Agreement (MTA) or Data Use Agreement (DUA).
- ***Funding status:*** Enquiries may be made of the Research Management Group ([RMG](#))/Office of Sponsored Research ([OSR](#)), to verify whether there is active funding.

Interaction

Several groups provide a vehicle for interaction among key individuals who are responsible for human research participant protection:

- ***VA/Stanford Working Group:*** Comprised of representatives of the VAPAHCS, and the Stanford RCO, who report back to their respective senior management.
- ***Privacy Governance Council:*** Convened by Stanford University Privacy Officer to explore issues related to implementation and enforcement of Privacy and Security rules under HIPAA.
- **[Stanford Center for Clinical and Translational Research and Education \(Spectrum\):](#)** Spectrum serves faculty and clinical research personnel at Stanford: in the School of Medicine, Stanford University Medical Center, Lucile Packard Children's Hospital (LPCH) and Veterans Affairs Palo Alto Health Care System (VAPAHCS).

Spectrum is an interdisciplinary center that facilitates health research across the university. Its core mission is to accelerate the translation of basic scientific discoveries into practical solutions that improve human health, through educational programs, research support, infrastructure streamlining and innovation funding.

Spectrum is a member of the Clinical and Translational Science Award (CTSA) consortium, funded by the NIH National Center for Advancing Translational Sciences

(Grant: UL1 TR001085). To help advance the nation’s health-research environment, Spectrum is working with the consortium to foster broad coalitions and partnerships at local and national levels.

Policies Available to all Parties to Research

The HRPP Policy Manual and other relevant policies and procedures are available to the sponsors and to the entire Stanford research community, including researchers, research staff, IRB staff, IRB members, employees, and students through the [Human Subjects Research website](#) and various other sources as described in [Chapter 3.1](#).

Ch. 3: Compliance Monitoring

3.1 Policies, Procedures, and Resources Available to Investigators and Research Staff

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

The Research Compliance Office (RCO) has primary responsibility for ensuring the [HRPP Policy Manual](#) and related materials are available to the entire Stanford research community, including:

- Investigators
- Research staff
- IRB staff
- IRB members
- Employees
- Students

The RCO maintains the [Human Subjects Research website](#) which provides access to:

- The [HRPP Policy Manual](#)
- Links to pertinent governmental regulations and guidelines
- Links to Stanford policies (Research Policy Handbook, Hospital and Clinic Policies, Lucile Packard Children's Hospital Policies and the VHA Handbooks and Directives)
- Guidance on various topics, such as sponsor-investigator research, children in research, use of test articles and reportable events
- Guidance on additional requirements when research is supported by, or under the purview of, agencies such as Departments of Defense, Education, Energy, and Justice; EPA; ICH-GCP; National Science Foundation; PHS
- IRB forms, including checklists, consent form and HIPAA authorization templates
- Protocol Application instructions and information
- Frequently Asked Questions and Practice Tips for investigators regarding human subject research protections and the IRB review process
- Human subject determination information and forms to assist investigators in identifying which protocols involve human subject research requiring IRB review. For example, the following might not be research under 45 CFR 46, or 21 CFR 50, 56:

QA/QI, pilot projects, research practicum, case studies (approximately 3 to 5), and oral histories. See [Is My Project “Research”?](#)

- New alerts highlighting the posting of new information or changes in existing policies and procedures
- IRB education presentations

The IRB staff is readily available by telephone and in-person meetings to assist investigators and research staff on human subject research matters, particularly IRB applications and review questions.

IRB member and staff education is provided at each convened IRB meeting. At the beginning of each meeting the IRB staff provides an educational presentation on a specific policy or procedures governing human subject research. Each monthly education presentation is also available to all IRB members on the [Human Subjects Research website](#).

The IRB staff regularly give presentations, often to large research groups, and accept invitations to attend classes and departmental meetings to provide information and guidance to the Stanford research community on IRB policies and procedures governing human subject research.

Within the RCO, the IRB staff is responsible for identifying new information involving human research participant protection such as new organizational policies, or emerging ethical and scientific issues. Information about new or modified laws might also be identified by legal counsel. New information is posted on the [Human Subjects Research website](#) and is disseminated to the IRB staff, IRB members and the Stanford research community via other distribution sources as noted above.

3.2 Independence of IRBs

Stanford has and follows written policies and procedures that allow the Institutional Review Board to function independently of other organizational entities in protecting research participants. (AAHRPP Element I.1.C)

Organizational Structure that Provides Independence

The President of Stanford University has delegated the authority and responsibility to establish, maintain and oversee the HRPP to the Vice Provost and Dean of Research as specified in the President’s [Delegation of Authority](#) letter.

The Vice Provost and Dean of Research, the Office of the Vice Provost and Dean of Research, and the RCO, which includes the IRBs and reports to the Vice Provost and Dean of Research, are separate from, independent of, and have no direct reporting relationship to any part of Stanford that carries out research or to any of the other organizations covered by the HRPP. The duties of the Vice Provost and Dean of Research and the Office of the Vice Provost and

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Dean of Research relate to establishing policy for research and oversight of research compliance, particularly as it relates to human participant research.

Delegation to the IRB

The Vice Provost and Dean of Research delegates independence and authority to the IRBs through this [Chapter 3.2](#) and the Charge to each IRB Chair ([medical](#) and [nonmedical](#)) and member at the time of their appointment. The IRBs have authority to:

- Review, approve, disapprove, or require changes in research involving human participants
- Suspend or terminate research involving human participants or an investigator's privilege to conduct such research (e.g., in situations where research is not being conducted in accordance with IRB requirements, or where the research has been associated with unexpected serious harm to participants)
- Observe, or have a third party observe the consent process
- Observe, or have a third party observe the conduct of research.

Prohibition against Others Usurping IRB Approval Authority or Using Undue Influence

The Vice Provost and Dean of Research prohibits Stanford officials, investigators, and employees, and sponsors contracting with Stanford for research from:

- Maintaining or claiming IRB approval of research that has been disapproved or not yet been reviewed by the IRB
- Attempting to use or using undue influence with the IRB, any of its members or staff, a PD, 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 the IRB or to influence an IRB member or staff, a PD, 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 IRB or one of its members or staff.

To help forestall undue influence of IRB members, the IRB preserves the anonymity of members assigned as reviewers to specific protocols or protocol events.

An individual who believes he or she has been subjected to such undue influence should make a report of non-compliance under [Chapter 3.9](#) (e.g., to the Research Compliance Director or Vice Provost and Dean of Research). Such reports will be reviewed in the same manner as possible non-compliance by an IRB Chair or member by the Vice Provost and Dean of Research as described in [Chapter 3.9](#). The types of response to attempts to unduly influence the IRB are

determined as appropriate to the situation, by either the Research Compliance Director or Vice Provost and Dean of Research.

3.3 Regulatory Definition of Human Subject Research

Human subject research is defined under 45 CFR 46.102(e) and (l), and 21 CFR 50.3 (c), (e) and (g). See also [VHA Directive 1200.05](#).

The IRB retains ultimate authority to determine whether an activity meets the definition of human subject research. Upon receipt of a [Human Subjects Research \(HSR\) Determination](#), IRB staff make this determination in a timely manner, and communicate to the PD their decision on whether the activity meets the definitions as defined in the HRPP Policy Manual.

[Chapter 1.4](#) describes the types of human subject research conducted at Stanford.

All protocols involving both "research" and "human subjects" (other than those determined to be exempt) must be reviewed and approved by the IRB before recruitment and data collection may start. See:

- Human Subjects Research website topic [Human Subject Research](#)
- Is My [Project](#) "Research"?
- [Does My Research involve Human Subjects?](#)

Pilot Studies

Stanford University and the VA have different definitions for pilot studies.

The Stanford Research Policy Handbook defines a pilot study as a preliminary investigation of the feasibility of a study, usually done on a small scale (usually fewer than 10 subjects) and exploratory in nature. It is designed to help the investigator refine data collection procedures and instruments or prepare a better, more precise research design. At the point of academic discussions, e.g., "how could this survey question be misunderstood?" such a pilot would not contribute to generalizable knowledge and therefore is not considered research and does not require IRB review. See RPH 5.4 [Use of Human Subjects in Student Projects, Pilot Studies and Oral Histories \(Non-Medical\)](#).

VA Research: Pilot studies are full-fledged research studies that must be approved by the IRB(s), when human subjects are involved. They are not considered to be activities preparatory to research. (See [VHA Directive 1200.05](#))

Stanford has and follows written policies and procedures for determining when activities are overseen by the Human Research Protection Program. (AAHRPP Element I.1.A)

Additional Requirements

Depending on the source of support for research, regulations from other agencies such as DOJ, etc. might apply. See [Other Federal Agencies - Additional Requirements](#) [GUI-42].

3.4 Exempt Research Determinations

The IRB has and follows written policies and procedures for determining when activities are exempt from applicable laws and regulations, when permitted by law or regulation and exercised by the IRB. Such policies and procedures indicate that exemption determinations are not to be made by Researchers or others who might have a conflict of interest regarding the studies. (AAHRPP Element II.2.A)

Categories of exempt research are stipulated in the Common Rule, Subpart A of 45 CFR 46. Exempt research is minimal risk to participants. See [45 CFR 46.104\(d\)](#), and [21 CFR 56.104](#) (FDA), [38 CFR 16](#) (VA), and guidance [Exempt Review Categories](#) [GUI-4].

Exempt status shall not be granted when the research involves:

- prisoners as participants, EXCEPT for research aimed at involving a broader subject population that only incidentally includes prisoners
- children in category 1, EXCEPT for educational tests or the observation of behavior when the investigator does not participate in the activities being observed
- children in category 2, EXCEPT for educational tests or the observation of public behavior when the investigator does not participate in the activities being observed under paragraphs (2)(i) and (ii);
 - paragraph (2)(iii) may not be applied to children
- children in category 3.

IRB Managers refer to guidance [Exempt Review Categories](#) [GUI-4] and use the [Exemption Eligibility Checklist](#) to verify that the PD has requested an appropriate exemption under the appropriate category.

Confirmation of exempt status is made by IRB members or designated IRB staff who have the knowledge and authority to confirm exemption. If a protocol meets the criteria for exemption, a [Notice of Exempt Review](#) is generated and is available for the PD. This notice indicates category(ies) under which the exemption is granted.

Emergency use of a test article is exempt from prospective IRB review under 21 CFR 56.104. See [Chapter 5.8](#) for more information on this topic.

Making Exemption Determinations without Conflict of Interest

Those IRB members, staff, and consultants involved in reviewing and approving the exempt determination of protocol applications must not participate in the review of protocols in which they have a conflicting interest – see [Chapter 6.6](#) for policies prohibiting such situations.

Emergency use of a test article is exempt from prospective IRB review under 21 CFR 56.104. See [Chapter 5.9](#) for more information on this topic.

3.5 Policies and Procedures for Exempt Research

The IRB has and follows written policies and procedures for addressing protection of participants in research that is exempt from applicable laws and regulations. These functions may be delegated to an entity other than the IRB. (AAHRPP Element II.2.B)

The IRB or EC has and follows written policies and procedures to conduct limited IRB or EC review, if such procedure is used. (AAHRPP Element II.2.C)

Stanford requires protocols qualifying for exempt review to be submitted for IRB review and confirmation of exempt status. While such research is exempt from the regulations set forth in 45 CFR 46.104(d), and 21 CFR 56.104 (FDA), and 38 CFR 16.104(d) (VA), the research must meet Stanford HRPP ethical standards governing the conduct of research. See [Chapter 1.6](#).

The IRB ascertains that exempt protocols provide appropriate protection of privacy and confidentiality interests (see [Chapter 11](#)).

If there are interactions with participants, requirements for the consent process apply to exempt research, such as providing the following information:

- The activity involves research
- A description of the procedures
- Participation is voluntary
- Name and contact information for the investigator.

Exempt Review Process

PDs are required to submit the Exempt Application Form in eProtocol. In reviewing the application, IRB staff refer to guidance [Exempt Review Categories](#) [GUI-4] and use the [Exemption Eligibility Checklist](#) to verify:

- whether the PD has requested an appropriate exemption, and
- that exemption, if granted, is assigned under the appropriate category.

The review is performed by IRB staff or IRB members who have the knowledge and authority to confirm exemption or refer the protocol for expedited or regular review.

For research involving Exempt categories 2(iii) and 3(i)(c) an IRB member will conduct a limited IRB review to ensure that there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data. Limited IRB review cannot be disapproved by the reviewer (it may be determined the study needs to be under expedited review or referred to full board). If the research is to be conducted at or by the VAPAHCS, it must also be approved by the VA Information System Security Officer/Privacy Officer and the VA Research & Development Committee.

If a protocol meets the criteria for exemption, a [Notice of Exempt Review](#) is generated and is available for the PD. A protocol will remain Exempt unless it is revised so that the criteria for Exemption are no longer satisfied.

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If a protocol does not meet criteria for exemption, it is returned to the PD with notification of failure to meet the criteria. As appropriate, the application is converted to a Protocol Application for expedited or regular review.

Once a protocol is determined to be exempt, it is not reviewed again unless a modification application is submitted. There is no continuing review process for exempt research, however, every three years researchers are asked to confirm the study is active.

3.6 Federal versus State Requirements

Stanford has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws. (AAHRPP Element I.1.G)

The IRB requires that PDs comply with the local, federal, and state laws that are applicable to their research.

A primary responsibility of the legal counsel to the IRB, who is a non-voting member of the IRB, is to provide advice to investigators and the IRB about such laws, particularly compliance with state laws while acting in accordance with the Common Rule and FDA regulations, and to assist in resolving any conflicts among applicable laws.

As needed, and in consultation with legal counsel, if necessary, IRB staff develop educational materials for investigators, IRB members, and staff relating to new state laws. Examples of such materials are the guidance [Research Surrogate Decision Makers](#) [GUI03032] which explains California law, and [Consent for Protocols Involving Children and Consenting Minors](#) which includes the definitions for “guardian” under California law.

California Health and Safety Code

See [Chapter 12](#) for situations under California Law which have additional requirements regarding the informed consent process when certain procedures and uses are involved, and for disclosure requirements for HIV testing under CA Health & Safety Code Section 121080.

California Law Exception

Health & Safety Code section 24178(a):

“Except for this section and the requirements set forth in Sections 24172 and 24176, this chapter shall not apply to any person who is conducting a medical experiment as an investigator within an institution that holds an assurance with the United States Department of Health and Human Services pursuant to Part 46 of Title 45 of the Code of Federal Regulations and who obtains informed consent in the method and manner required by those regulations.”

Laws of Other States (Research Outside of California)

Stanford investigators conduct research in states other than California. As each state has different laws, Stanford investigators are expected to adhere to the laws of the state in which research is being conducted as well as those of California.

When necessary other attorneys in the Office of the General Counsel or outside attorneys retained by it can provide direction and interpretation of California and other state's laws.

3.7 Investigators' Conflicts of Interest (COI)

Stanford has and follows written policies and procedures to identify, manage, and minimize or eliminate individual financial conflicts of interest of Researchers and Research Staff that could influence the conduct of the research or the integrity of the Human Research Protection Program. The Organization works with the Institutional Review Board in ensuring that financial conflicts of interest are managed and minimized or eliminated, when appropriate. (AAHRPP Element I.6.B.)

Policies for Faculty

Stanford University has the following policies regarding conflict of interest (COI) for research carried out at Stanford University, Stanford Hospital and Clinics (SHC), Lucile Packard Children's Hospital (LPCH), the VAPAHCS, or elsewhere:

- Stanford University Research Policy Handbook (RPH):
 - RPH 4.1 [Faculty Policy on Conflict of Commitment and Interest](#), and
 - RPH 4.2 [PHS and NSF Requirements Regarding Financial Disclosures and Agency Notifications](#).

School Deans are responsible for ensuring implementation of the Faculty Policy on Conflict of Commitment and Interest; the Vice Provost and Dean of Research is responsible for interpretation and overall coordination of the policy.

Policies for Staff and Students

Policies for staff and students are found at:

- RPH 4.4 [Conflict of Interest and Commitment For Academic Staff and Other Teaching Staff](#)
- Administrative Guide Memo 1.5.2 [Staff Policy on Conflict of Commitment and Interest for staff members](#)
- RPH 10.6 [Relationships Between Students \(including Postdoctoral Scholars\) and Outside Entities](#)

Disclosure of Financial Interests

Faculty must disclose on an annual basis all financial relationships that reasonably appear to be related to their institutional responsibilities. This is done through Stanford's Outside

Professional Activities Certification System (OPACS). In addition, as faculty enter into changed or new financial relationships related to their institutional responsibilities, they can access their OPACS disclosures to update previously reported activities or financial relationships, or to enter new activities.

When potential conflicts of interest relate to human subject research protocols, they require a transactional (ad hoc) disclosure in OPACS. Disclosure must be made by each investigator for him or herself and his or her immediate family. “Immediate family” means the investigator’s spouse or domestic partner and dependent children (as defined by the IRS).

Management of conflicts of interest is vested in the offices of the School Deans at Stanford University. The Vice Provost and Dean of Research is the University officer responsible for interpreting and overseeing implementation of and compliance with this policy.

Before a protocol application can be submitted to the IRB, the Protocol Director, faculty listed on the protocol, and any others identified as presenting a potential conflict of interest must answer the screening questions in OPACS.

Management of Investigator Conflict of Interest Disclosures

If one of the investigators on a protocol has answered “yes” to one of the screening questions, the case is managed in accordance with university policies. The [Managing Conflicts of Interests](#) website discusses questions for the investigator and the institution to consider when assessing COI.

All investigators’ conflicts of interest (for all schools, including SOM) are reviewed via the Conflict of Interest Review Program (COIRP).

Conflict disclosure in the informed consent process may be an important part of the management strategy but will not necessarily be the only strategy used. It is the responsibility of the COIC to determine what strategy or strategies are appropriate to eliminate, mitigate, or manage conflict that has the potential to compromise the objectivity of the research.

Role of the IRB

Review of Potential Investigator Conflicts of Interest

When a potential conflict of interest has been identified by the COIRP, the IRB communicates closely with the appropriate COI point of contact and the investigator throughout the protocol review process. When appropriate, a plan or strategy to adequately eliminate, mitigate, or manage the conflict must be determined by the COIRP and accepted by the IRB. See [Chapter 14.1](#). The COI Manager fills out a Transaction Assessment Report that informs the IRB of the COIC evaluation including any management plan. The IRB has the final authority to decide whether the potential conflict of interest and its management, if any, allows the research to be approved.

- When there are non-substantive outstanding COI matters, a protocol may be approved contingent upon the matters being resolved.
- When there are substantive outstanding COI matters, a protocol will either be tabled or precluded from possible approval until matters are resolved.

Only when COI matters are completely resolved is the protocol Approval Letter generated.

Review of Conflicts of Interest Disclosed after IRB Approval of Research

When a potential conflict of interest arises and the investigator discloses it after the IRB has reviewed and approved a protocol, the investigator should immediately notify the IRB of the potential conflict and notify the IRB that enrollment and protocol procedures will stop until the conflict of interest has been reviewed and resolved by the COIC as described above. The determination by the COIC is forwarded to the IRB.

When a known potential conflict of interest is discovered after the IRB review and approval, the IRB will ask the PD to file a conflict of interest disclosure in OPACS as described above, and may, among other possible actions, ask the investigator to disclose the relationship to research participants.

Recordkeeping

Records on all disclosures of financial interests and all decisions to manage, reduce, or eliminate conflicts of interest are maintained for three years from the date of final disclosure. This information will be made available to DHHS upon request, while maintaining the confidentiality of all records of financial interest.

Other Agency Requirements

VA research: Veterans Affairs Palo Alto Health Care System (VAPAHCS) Memorandum No. 151-14-14 Research Financial Conflict of Interest Disclosures defines policies and procedures regarding conflict of interest as defined in this memorandum.

Additional Requirements

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy), or particular requirements regarding financial disclosures and agency notifications (e.g., if the research must follow Public Health Service (PHS) or National Science Foundation (NSF) regulations): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

3.8 Institutional Conflict of Interest

Stanford has and follows written policies and procedures to identify, manage, and minimize or eliminate financial conflicts of interest of the Organization that could influence the conduct of the research or the integrity of the Human Research Protection Program. (AAHRPP Element I.6.A)

The policy is found in the Research Policy Handbook, RPH 4.7 [Institutional Conflict of Interest in Research Involving Human Subjects](#). An institutional conflict of interest (ICOI) is created if an investigator at Stanford undertakes to do human subjects research on a drug, device, biologic, or other item on which Stanford has a patent, has licensed the intellectual property, or receives royalties or other fees. All new human subjects research protocols submitted for IRB review must indicate the source(s) of all funding to be used in supporting the research, including unrestricted school, department, or individual accounts, as well as the name of the manufacturer when applicable. In addition, the investigators are required to answer questions about the relationship of their research to their administrative duties. When a protocol lists a manufacturer, or when other information indicates a potential conflict, the issues are handled as outlined in RPH 4.7 [Institutional Conflict of Interest in Research Involving Human Subjects](#). Decisions are communicated to the IRB, to the relevant offices within the University, and to the relevant dean or associate dean so that the recommendations can be implemented at the level of the individual schools as appropriate.

Role of the IRB

Review of Potential Institutional Conflicts of Interest

When a potential institutional conflict of interest has been identified, the IRB provides the ICOI informed consent template language to the researchers to update the consent document. When appropriate, a plan or strategy to adequately eliminate, mitigate, or manage the conflict must be determined by the ICOIC and accepted by the IRB.

3.9 Non-Compliance with HRPP Requirements

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

Stanford has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements, and works with the Institutional Review Board, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate. (AAHRPP Element I.5.D)

Any situation of perceived or actual serious or continuing non-compliance jeopardizes the Stanford commitment to human subject research protection. Receiving information about possible non-compliance is essential for accountability and education purposes, correcting non-compliance, deterring it from occurring again, and attempting to mitigate any adverse effects or harm on research participants, or compromising their welfare.

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Definitions

Non-compliance:

An action, inaction, or activity, whether by the investigator, study staff, or others involved in human subject research, that is at variance with the approved IRB protocol, other requirements and determinations of the IRB, the HRPP Policy Manual and other applicable policies of Stanford University, SHC, LPCH, VAPAHCS (e.g., [VHA Directive 1200.05](#)), Palo Alto Veterans Institute for Research (PAVIR) or relevant state or federal laws.

The following are always considered noncompliance:

- human subjects research conducted without IRB approval, or approved by an outside IRB, without prior notice to Stanford's IRB (or Stanford IRB approval, if required under Stanford policies); or
- change(s) to the research implemented without IRB approval except when necessary to eliminate apparent immediate hazards to the subject.

Serious non-compliance: Any behavior, action, inaction, or omission in the conduct or oversight of human research that, in the judgment of the IRB, has been determined to:

- adversely affect or compromise the rights or welfare of participants;
- harm or materially increase exposure to significant risk of harm to a research participant (the IRB does not have to find that harm has occurred, or was likely to occur, to make a determination of serious noncompliance);
- result in a detrimental change to a participant's clinical or emotional condition or status; or
- compromise the integrity or validity of the research.

Continuing non-compliance: A pattern of repeated instances of noncompliance that:

- continues to occur after discovery of noncompliance or implementation of a preventive action plan; or
- results from failure to implement a preventive action plan approved by the IRB; or
- a circumstance in which an investigator or other study staff fails to cooperate with investigating or correcting non-compliance.

VA research: The definitions of serious and continuing non-compliance are defined in [VHA Directive 1058.01](#) - Research Compliance Reporting Requirements.

Allegation of non-compliance: A report of non-compliance that represents an unproven assertion.

Finding of non-compliance: Non-compliance that is true, or an allegation of non-compliance that is determined to be true based on a preponderance of the evidence.

Obligation to Report Non-Compliance

Allegations, observations, or evidence of non-compliance in human subject research must be reported to the Research Compliance Office by:

- Protocol Director (PD) or any research team member
- Employee of Stanford
- IRB member or Research Compliance Office (RCO) staff
- Study monitor, auditor, or sponsor either directly or through the PD.

Non-compliance can be reported to the RCO by the PD on the eProtocol Report Form (self-reported) or by other individuals (may be done anonymously) via telephone, email, or letter. IRB members and IRB staff may also identify non-compliance or possible serious and/or continuing non-compliance during the course of protocol review, e.g., continuing review, modifications, informed consent reviews. If identified, the IRB staff will direct the PD to report the non-compliance to the IRB on the eProtocol Report Form for further review by the IRB. Reports of non-compliance, not self-reported on the eProtocol Report Form, are recorded by the RCO staff and are investigated in the same manner as those reported in eProtocol.

Research participants and individuals not directly involved with conducting or overseeing the research are also encouraged to report suspected non-compliance.

Reports of possible non-compliance may also be directed to the following individuals, who in turn forward them to the RCO staff:

- The PD
- The Vice Provost and Dean of Research
- Internal Audit: oversight of Institutional Compliance at Stanford resides under the Associate Vice President for Audit, Compliance and Privacy. Reports can be submitted anonymously through the [Helpline Request](#), or [emailed](#).
- ***For research in the VAPAHCS system:*** Members of the VA research community must report possible non-compliance in writing to the IRB within five business days after becoming aware of it and must also report in the same time frame directly to the Medical Center Director, VAPAHCS Associate Chief of Staff for Research and Development, and other relevant research review committees as appropriate.

Non-Compliance – Allegations or Findings

Reports can be either allegations or findings of non-compliance. Allegations of non-compliance that have yet to be proven are reviewed and investigated. An allegation determined to be true based on a preponderance of the evidence becomes a finding. Generally, self-reported instances by investigators on the Report Form will be accepted as a finding of non-compliance.

Review of Allegations or Findings of Non-Compliance

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All reports or allegations of findings of non-compliance are initially evaluated by the IRB staff. An initial report will either be designated as not requiring further action or will be escalated for review by the RCO Director or their delegate. If a report is an allegation, the RCO Director or delegate will review the report. See [Process for Addressing Allegations and Findings of Non-Compliance](#).

A report requires no further action if the non-compliance is:

- Neither serious nor continuing; and
- Addressed by the investigator through a corrective action plan to remedy the matter.

If a report of non-compliance does not require further action, the incident and corrective action plan will be documented, reviewed by the Chair or experienced IRB member, and stored.

For reports that are escalated for review, the RCO Director or their delegate ensures that immediate action is taken as necessary to prevent unacceptable risk to research participants. For non-compliance that is possibly serious or continuing (in the opinion of the RCO Director or their delegate), the RCO Director reports orally or by email within five business days to the Vice Provost and Dean of Research or other senior leadership, as appropriate, and subsequently provides updates on fact-finding and IRB review process. Findings of possible serious and/or continuing non-compliance are referred to the IRB for further review.

Investigation

The RCO Director or delegate reviews the report and chooses one of the following courses of action in investigating the allegation:

- Conducts the review alone
- Conducts the initial review in co-ordination with the IRB Chair
- Delegates some or all of the review to IRB and/or Continuous Quality Improvement staff
- Empanels a subcommittee of the IRB
- Requests that legal counsel provide advice and conduct the review,
- Requests assistance from others at Stanford, e.g., Office of Internal Audit, Office of General Counsel, a non-involved Stanford University or VA physician as an expert, or outside consultants.

The individual(s) or subcommittee conducting the investigation will interview the individuals(s) involved in the allegation and others that can contribute to the discussion. Any of the following necessary actions may be taken to determine whether allegations are true and to determine the seriousness or number of occurrences of the actions:

- Review written materials

- Interview knowledgeable sources
- Collect relevant documentation.

During the fact-finding process, the RCO Director or delegate communicates as appropriate with the PD or representative about the progress of the review and investigation. A record of findings and evidence is made by the RCO and stored in the appropriate files.

Allegations which, in the opinion of the RCO Director or delegate and the IRB Chair or experienced IRB member, are supported by the preponderance of evidence are determined to be findings of non-compliance.

If the non-compliance is neither serious nor continuing, the RCO Director or delegate, alone or with the IRB Chair or experienced IRB member, examines whether the PD understands the non-compliance and, if appropriate, has an adequate corrective action plan. If so, the decision and corrective action plan are documented and filed, otherwise the report is referred to the IRB (the convened IRB, the IRB Chair, or their delegate) for further review (see [Internal and External Reporting](#)).

Findings of non-compliance are assessed by the RCO Director or delegate and the IRB Chair as to whether they are either serious or continuing.

For research in the VAPAHCS system: Upon receipt of a report of possible serious and/or continuing non-compliance on a VA human subjects research project, the IRB will review such reports at the earliest practicable opportunity, not to exceed 30 business days after receipt. The IRB Chair may take interim action to eliminate apparent immediate hazards to participants.

Serious or Continuing Non-Compliance Referred to the IRB

Non-compliance that is believed to be serious or continuing is referred for review by the convened IRB. The PD or representative is informed that the possible serious or continuing non-compliance will be brought before the IRB.

The IRB receives the report describing the non-compliance and considers the information provided in the non-compliance report, all relevant information (e.g., the protocol, risks to participants, materials from the investigation, history of non-compliance, audit or monitoring findings), and the draft corrective action plan from the PD.

As a result of this review, the following actions may be taken:

- The IRB determines that additional information is needed and requests that such information be obtained before further action is taken.
- The IRB determines that non-compliance did not occur or that non-compliance occurred, but was neither serious nor continuing, and either takes no action or takes action appropriate to the situation (see possible actions below).

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- The IRB determines that non-compliance occurred and that it was serious or continuing. This is referred to as a “Reportable Decision” (see [Chapter 3.11](#)), and the IRB:
 - Takes action appropriate to the situation (see possible actions below)
 - Follows the internal reporting procedure required in [Chapter 3.11](#) concerning determinations of serious or continuing non-compliance.
- For concerns not within the IRB’s purview, including some sanctions pertaining to faculty or students, the IRB refers the matter to the appropriate officials at Stanford University, SHC, LPCH, or VAPAHCS.

IRB determinations and actions are recorded, and communicated to the PD, and as appropriate to the relevant, involved individual(s). IRB determination reports of serious or continuing non-compliance are reviewed by the PD for factual errors prior to being reported internally and externally as described in [Chapter 3.11](#).

Possible IRB Actions for Serious or Continuing Non-Compliance

In considering actions for serious or continuing non-compliance, the IRB seeks to:

- Correct the non-compliance
- Deter it from occurring again (e.g., hold the relevant individuals accountable for their actions and provide education on how to comply), and
- Attempt to mitigate any adverse effects or harms on participants, or any compromise of their welfare.

The IRB will consider:

- Suspension or termination of the protocol pursuant to [Chapter 9.4](#)
- Notification of current participants (required when such information may relate to participants’ willingness to continue to take part in the research)

Other possible IRB actions include but are not limited to the following:

- Additional corrective actions
- Changes to previously approved protocol and consent forms
- Modification of the information disclosed during the consent process
- Requiring re-consent of current participants to continued participation
- Change in PD
- Monitoring of the research
- Monitoring of the consent process

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- Referral to other organizational entities (e.g., legal counsel, risk management, institutional official, School Dean, Department Chair)
- Provision of additional information to past participants
- Modification of the continuing review schedule
- Participation by research team members in additional training or education
- When appropriate, applying any corrective action to all similar protocols.

If the IRB action will affect participants in the protocol (e.g., requires withdrawal of participants), the IRB utilizes a process that takes into account the impact on their health and safety as described in [Chapter 9.4](#).

Additional Requirements

Other Federal Agencies

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for requirements depending on the source of support/funding (e.g., Department of Defense, Department of the Navy).

VA research

When the IRB makes a determination of serious and/or continuing non-compliance at a convened meeting, the IRB will notify the VA of the determination. The notification will be made within 5 business days of the date of the determination and will include the Principal Investigator, the VA Facility Director, the Associate Chief of Staff for Research, the Research Compliance Officer, and the Human Protections Administrator. Refer to [VHA Directive 1058.01](#) for VA definitions, and timelines for IRB determinations and remedial actions.

IRB-Related Non-Compliance Involving an IRB Chair, IRB Member or RCO Staff

IRB Chairs, IRB Members or RCO Director

The Vice Provost and Dean of Research is primarily responsible for investigating and reviewing IRB-related non-compliance involving an IRB Chair, IRB member or the RCO Director. If a fact-finding review of an allegation is necessary to assess the evidence, it could include the Vice Provost and Dean of Research acting alone, delegating some or all of the review to IRB staff, empaneling a review committee, requesting that legal counsel provide advice and conduct the review, or requesting assistance from others. The Vice Provost and Dean of Research finds whether the allegation is true. If the Vice Provost and Dean of Research makes a finding of serious or continuing non-compliance, the report is referred to the appropriate convened IRB for review.

Any disciplinary action must be taken in accordance with the Statement on Faculty Discipline approved by the Senate of the Academic Council and any other applicable provision of the Faculty Handbook and the Research Policy Handbook.

RCO Staff

The RCO Director is primarily responsible for reviewing non-compliance involving RCO staff and determining if allegations are supported by a preponderance of evidence. The RCO Director may delegate the initial review or fact-finding to others, such as the supervisor of the staff member. If the non-compliance is deemed to have merit the RCO Director is ultimately responsible for determining the action via Stanford policies and procedures: [Administrative Guide Memo 2.1.15, Trial Period](#), and [2.1.16, Corrective Action and Discipline](#).

Possible IRB Actions for Non-Compliance Involving an IRB Chair, IRB Member or Staff

Possible actions include but are not limited to the following, as appropriate:

- Education and Training
- Evaluation of the IRB Chair's or member's ability to serve on the IRB, or evaluation of the staff member's ability to support the IRB
- Revision of IRB policies and procedures for new content or clarifications to minimize the likelihood of repeated noncompliance
- Removing a staff member from certain responsibilities if the noncompliance was determined to be the result of inadequate expertise or skills
- Modification of the information disclosed during the consent process
- Provision of additional information to past participants
- Notification to current participants (required when such information may relate to participants' willingness to continue to take part in the research)
- Requirement to re-consent current participants to continued participation
- When appropriate, applying any corrective action to all similar protocols

3.10 Unanticipated Problems Involving Risks to Participants or Others (UPs), and Other Reportable Information

Stanford has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements, and works with the Institutional Review Board, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate. (AAHRPP Element I.5.D)

The IRB has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate. (AAHRPP Element II.2.G)

Definition

Unanticipated problems involving risks to participants or others (UPs):

Per [OHRP 2007 Guidance](#): A UP is any incident, experience, or outcome that meets the following criteria as discussed below:

- Is unexpected (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-related documents, such as the IRB-approved research protocol and informed consent document or the Investigator's Brochure; and (b) the characteristics of the subject population being studied;
- Is related or possibly related to participation in the research (, *possibly related* means there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and
- Suggests that the research places subjects or others at a greater risk of harm (e.g., physical, psychological, economic, or social harm, including harm related to breaches of privacy) than was previously known or recognized.

Protocol Director responsibilities for reporting unanticipated problems involving risks to research participants or others, and other reportable information, are outlined in [Chapter 15.2](#).

Events and Information – Required Reporting to the IRB

Events and information that must be reported to the IRB, along with the timelines for reporting, are listed in the guidance [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13]. They should be reported to the IRB using the online IRB Report Form in the eProtocol system.

VA Research – timeframe for reporting

Refer to [VHA Directive 1058.01](#) for requirements about report timelines and distribution for UPs, and termination or suspension of research.

Additional Reporting Requirements

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Energy, Department of Justice: National Institute of Justice (NIJ) and research conducted with the Bureau of Prisons): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

Optional Reporting

The IRB Report Form may also be used to report other items (category 7 in guidance [Events and Information that Require Prompt Reporting to the IRB](#)) [GUI-P13]– however, PDs should consult with IRB Education before reporting such items.

Review of Reports

See flowchart [Process for Handling Reports](#). At any point during the review process, the IRB staff, the IRB member, or the convened IRB may seek additional expertise if needed.

IRB Staff Evaluation

The IRB staff evaluates reports, checking whether reports have been appropriately completed (e.g., correct report category has been indicated; for events reported as UPs it is indicated that the event was unexpected, related and harmful; supporting documents have been submitted with the report). A report that does not satisfy initial IRB staff evaluation will be returned to the PD with an explanation.

IRB Member Review

Reports which appear to be UPs, and reports of other reportable events and information will be assigned to an IRB member with adequate expertise for review.

The IRB member reviews the report and materials from the protocol file, (e.g., protocol, investigator's brochure, continuing reviews, modifications, and other reports) and assesses whether the report constitutes a UP or other information that should be presented at an IRB convened meeting.

IRB Convened Meeting Review

Prior to the meeting, the IRB staff provides all voting members with a copy of the report and supporting documents.

At the convened meeting, the IRB discusses and votes on whether the report qualifies as a UP or other reportable information. The vote is recorded in the minutes for the meeting. The IRB considers whether any action is necessary, and the decision is documented in the minutes and in the protocol file.

Possible Actions by the IRB

The IRB has a range of available actions it can take if an event is deemed to be a UP or other reportable information. Depending on the severity of the event and the potential for continuing risk to participants, the IRB determines what further action will be required, including:

- Suspending the research
- Terminating the research
- Requiring participants to be notified of the event, especially if the event may relate to the participant's willingness to continue in the study

- Requiring a modification to the research (either as soon as possible or at continuing review). The modification can include a change to the study procedures, informed consent process or written informed consent document
- Requiring current participants to be re-consented
- Providing additional information to past participants
- Requiring monitoring of the research or consent process
- Modification of the continuing review schedule
- Referral to other organizational entities (e.g., legal counsel, risk management, institutional official)
- Other actions as deemed appropriate.

If the convened IRB:

- Determines that an unanticipated problem involving risks to participants or others (UP) or some other reportable event has occurred, or
- Suspends or terminates the approval of a protocol (see [Chapter 9.4](#)), or
- Determines that serious or continuing non-compliance has occurred (see [Chapter 3.9](#)),

this is designated a “Reportable Decision”, and internal and external reporting proceeds as outlined in [Chapter 3.11](#).

Any action taken by the IRB is communicated to the PD, and to the CCTO if a Cancer Center study. If the IRB action will affect participants in the protocol (e.g., requires withdrawal of participants), the IRB considers the impact on their health and safety. (See [Chapter 9.4](#).)

VA Research

The IRB Coordinator at the VA is notified electronically via eProtocol when a Report (possible UP, etc.) is submitted to the IRB for VA research.

Reports of serious unanticipated problems involving risks to participants or others, or of local unanticipated serious adverse events, will be reviewed and a determination made as specified in [VHA Directive 1058.01](#).

The IRB Coordinator at the VA is notified of any IRB action and is responsible for further reporting to the VA Director, and the Office of Research Oversight (ORO) as required. See [VHA Directive 1058.01](#).

Review of Gene Transfer SAEs

Gene Transfer Serious Adverse Event (SAE): A serious adverse event arising out of a gene transfer protocol as defined in NIH Guidelines I-E-8, I-E-9, and I-E-10.

See [NIH Guidelines for Research Involving Recombinant DNA Molecules](#).

For gene transfer protocols, PDs are instructed that all gene transfer SAEs occurring at Stanford and at other institutions must be reported to the Biosafety Panel. Any SAEs that meet the criteria for a possible [Unanticipated Problem](#) should also be submitted to the IRB in the eProtocol system.

3.11 Internal and External Reporting

Stanford has and follows written policies and procedures for addressing allegations and findings of non-compliance with Human Research Protection Program requirements, and works with the Institutional Review Board, when appropriate, to ensure that participants are protected when non-compliance occurs. Such policies and procedures include reporting these actions, when appropriate. (AAHRPP Element I.5.D)

The IRB has and follows written policies and procedures for addressing unanticipated problems involving risks to participants or others, and for reporting these actions, when appropriate. (AAHRPP Element II.2.G)

The IRB has and follows written policies and procedures for suspending or terminating IRB approval of research, if warranted, and for reporting these actions, when appropriate. (AAHRPP Element II.2.H)

Reportable Decisions

If the convened IRB:

- determines that serious or continuing noncompliance has occurred as specified above under [Chapter 3.9](#), or
- determines that an unanticipated problem involving risks to participants or others (UP) or some other reportable event has occurred as specified in [Chapter 3.10](#), or
- suspends or terminates the approval of a protocol pursuant to [Chapter 9.4](#)

the IRB Chair and the RCO Director send the Reportable Decision to the Vice Provost and Dean of Research. See [Report Handling Process](#) flow chart. Written procedures for reporting unanticipated problems, noncompliance, suspension, and termination follow the OHRP and FDA regulations (45 CFR 46.108(a)(4); 21 CFR 56.108(b)).

Additional Reporting Requirements

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

Timeline for and Content of Report

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An oral report by the RCO Director about the Reportable Decision will be made to the Vice Provost and Dean of Research within five business days. The IRB will provide a notification to the Vice Provost and Dean of Research generally within 30 days of the IRB's determination.

The notification will cover the IRB findings and any applicable actions as well as supporting documents as applicable. For VA reportable decisions, notification and reporting timeframes are as described in VHA Directive 1058.01.

Distribution

The reports are sent to the following:

- For all non-exempt human subjects research, report to the sponsor, the Institutional Official, and the Protocol Director, and relevant officials of SHC, LPCH and VAPAHCS including
 - The relevant privacy officer, if the report involves any unauthorized use, loss or disclosure of HIPAA protected health information as described in [Chapter 11](#)
 - The relevant security officer, if the report involves a violation of the HIPAA electronic security requirements for protected health information as described in [Chapter 11](#)
 - Any other individuals who the Vice Provost and Dean of Research, the IRB Chair or RCO Director choose to notify (e.g., School Deans, Department Chairs, Division Chiefs, VA administrators, the Office of the General Counsel).
- For research that is HHS supported or conducted, or by a Federal Agency that has adopted the Common Rule (unless the Agency approved a separate assurance other than the FWA for the research), we follow the 2011 Guidance on Reporting Incidents to OHRP and also report to the relevant HHS Department or Agency, and to OHRP on the [OHRP Incident Reporting Form](#);
- For research that is subject to the Food and Drug Administration regulations regarding human subjects (any activity that involves an approved or unapproved drug or medical device except for activities that involve the use of an approved drug or medical device in the course of medical practices, and any activity in which data is reported to or held for inspection by FDA), we report to the FDA.
- For research that is HHS supported or conducted, or by a Federal Agency that has adopted the Common Rule (unless the Agency approved a separate assurance other than the FWA for the research), **AND** research that is subject to the Food and Drug Administration regulations regarding human subjects (as detailed above), we report to both OHRP **AND** FDA.

Written reports will be sent as soon as possible, but generally not longer than 30 days after the IRB determination. This may be an initial report that indicates that a follow-up or final report

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will follow by a specific date, when an investigation has been completed, or when a corrective action plan has been implemented. For more serious incidents, the RCO Director will make an oral or preliminary written report within five business days with an estimated time for the final report.

The report will include:

- The name(s) of the relevant Stanford organization(s) conducting the research
- The title and number of the IRB protocol and of any federal proposal or award in which the Reportable Decision occurred
- The name of the Protocol Director (PD) and the Principal Investigator (PI) on any applicable federal award if different from the PD
- A detailed description of the Reportable Decision
- The actions taken or planned to be taken to address the circumstance(s) leading to the Reportable Decision.
- HHS studies will be reported to OHRP on their [Incident Reporting Form](#)

For multicenter research projects, only the institution at which the participant(s) experienced an adverse event determined to be an unanticipated problem (or the institution at which any other type of unanticipated problem occurred) must report the event to the supporting agency head (or designee) and OHRP (45 CFR 46.108(a)(4)(i)) unless the study is reviewed under a sIRB; in this case, the Institutional Authorization Agreement will state which site reports externally.

Action by the VA Facility Director/Associate Chief of Staff for Research and Development and External Reporting

The VA Facility Director or Associate Chief of Staff for Research and Development either accepts the report or refers it back to the IRB for further information or consideration of other action.

Once the VA Facility Director and/or the Associate Chief of Staff for Research and Development are notified of any IRB determinations and action, they in turn report to the Office of Research Oversight (ORO), and to the appropriate Federal agency (e.g., OHRP, FDA, NIH, etc.) as stated in the [Memorandum of Understanding](#) between Stanford University and the VAPAHCS.

Notification and reporting timeframes are described in [VHA Directive 1058.01](#) and Local HCSM 00-15-32.

3.12 Assurance of Compliance

Stanford University and its affiliates maintain five Federalwide Assurances under OHRP (45 CFR 46.103), available to investigators and others involved in human subject research. See the Research Policy Handbook, RPH 5.2 [Federal-wide Assurance for Protection of Human Subjects](#).

3.13 HRPP Quality Improvement Activities

The Organization conducts audits or surveys or uses other methods to assess compliance with organizational policies and procedures and applicable laws, regulations, codes, and guidance. The Organization makes improvements to increase compliance, when necessary. (AAHRPP Element I.5.A)

The Continuous Quality Improvement (CQI) Program of the Research Compliance Office (RCO) is designed to:

- Evaluate and monitor the effectiveness of the HRPP,
- Assess compliance with HRPP policies and procedures,
- Identify areas and implement measures for improvement.

This is accomplished by working with the various components of the HRPP to design, recommend and implement improvements to promote the protection of human subject research participants.

Compliance Monitoring

HRPP staff conduct periodic compliance reviews and for-cause assessments to evaluate adherence to applicable federal regulations, state and local laws and Stanford policies and procedures, and to verify that research is conducted in accordance with the IRB approved protocols.

- **Periodic Compliance Reviews:** Periodic compliance reviews are conducted using systematic methods to assess investigator and IRB compliance with federal regulations, state and local laws, and Stanford policies and procedures. Periodic compliance reviews include but are not limited to:
 - Examinations of executed informed consent forms
 - Reviews of IRB meeting minutes;
 - Detailed examinations of protocol files;
 - Observations of the informed consent process.
- **For-cause assessments:** The HRPP Associate Director or the RCO Director may direct HRPP staff to conduct an assessment in response to a particular concern. Concerns that may prompt a for-cause assessment include but are not limited to:
 - Failure of routine reviews;
 - Complaints or concerns initiated by a research participant, family member, or research team/workforce member;
 - Reports of serious or repeated non-compliance;

- Results of reviews or monitoring conducted by other Stanford components (e.g., VA, Cancer Center DSMC, Internal Audit) are reported to designated HRPP staff.

Additional Requirements

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for other requirements depending on the source of support/funding.

Reporting of Compliance Monitoring Results

Results of compliance monitoring activities are documented and reported to the HRPP Associate Director, the RCO Director, the IRB, Institutional Officials, and other units within Stanford as appropriate. These results, supplemented by other review results when available, provide a quantitative and qualitative measurement of compliance with the HRPP.

Other Review Activities

Depending on the results of annual risk assessments, Stanford University's Internal Audit Department may conduct additional reviews of the IRBs and the various schools and departments within Stanford that conduct or review human subject research activities.

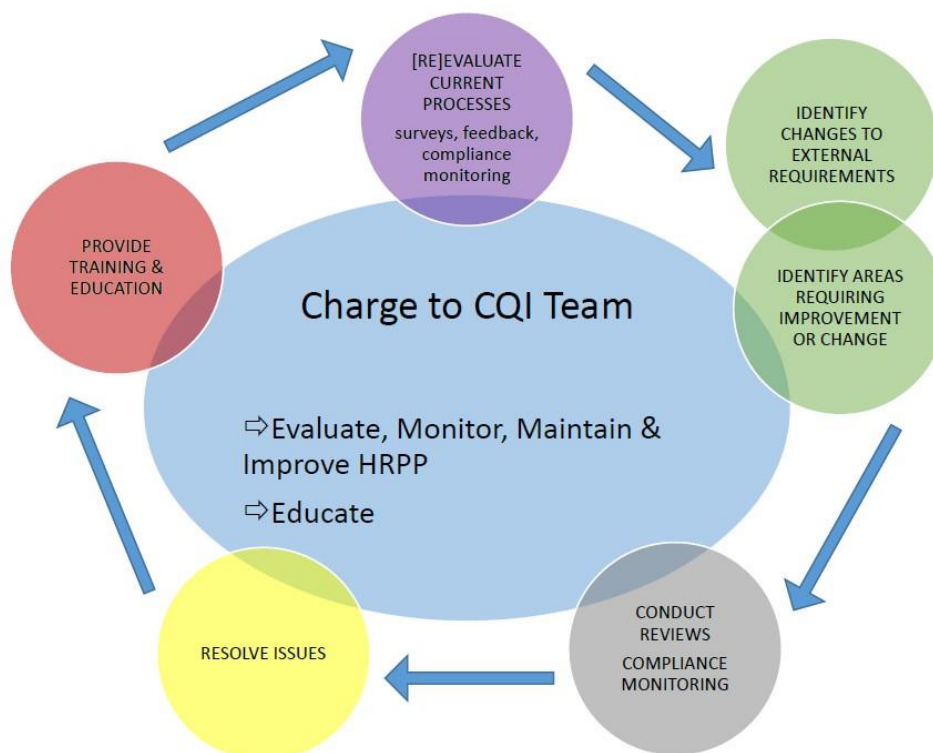
Research Community Feedback

HRPP staff track comments, questions and issues received from the Stanford investigators and participants to identify areas for potential improvement in the effectiveness of HRPP policies and procedures and for ensuring the protection of human subject research participants. The Protocol Director and key study personnel receive a request to respond to a survey after approval of each event by the IRB.

IRB Performance Metrics

HRPP staff produce periodic metrics and analysis of the IRB operations and functions, including detailed measurements of activity volume and processing times.

Continuous Quality Improvement (CQI)



Based on the results of the aforementioned assessments and feedback received from the communities served by the HRPP, the HRPP staff of the Research Compliance Office partner with other components of the Stanford HRPP to identify root causes of problems, recommend action plans to correct issues, and provide education, tools and outreach to promote effectiveness of improvements.

Significant changes to the Human Research Protection Program (HRPP) that are implemented as a result of quality assessment and quality improvement activities are monitored to ensure effectiveness and consistency.

This leads to the continuous improvement of the HRPP and the protection of human subject research participants.

See [Continuous Quality Improvement \(CQI\)](#) for more information on the CQI Program.

3.14 Investigators' Input to the HRPP

Stanford has and follows written policies and procedures so that Researchers and Research Staff may bring forward concerns or suggestions regarding the Human Research Protection Program, including the ethics review process. (AAHRPP Element I.5.C.)

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There are a variety of mechanisms available for contacting relevant individuals to bring concerns and suggestions, including:

- Reporting possible non-compliance as described in [Chapter 3.9](#)
- Reporting possible unanticipated problems as described in [Chapter 3.10](#)
- Making general comments and suggestions and expressing concerns about other matters, issues or processes involving the HRPP, including IRB review and operations to any person in the Research Compliance Office or in the Office of the Vice Provost and Dean of Research.
- Internal Audit: Institutional Compliance oversight resides under the Associate Vice President for Audit, Compliance and Privacy. As an additional safeguard to reporter privacy, such information can be submitted anonymously, if desired, through the [Helpline](#) Request found on the Internal Audit and Institutional Compliance [website](#), or emailed to compliance@stanford.edu)
- ***For research at the VAPAHCS:*** Members of the Chief of Staff's office or the Research and Development Committee.

In addition, input from researchers is actively sought for each protocol review on a continuing basis, via an ongoing survey about the service provided by the IRBs; researchers may comment or provide suggestions on any aspect of the IRB or HRPP, either anonymously or by requesting discussion with the Research Compliance Office. Aggregate [survey results](#) are published periodically on the Humans Subjects Research website.

The RCO Director receives and evaluates the input from any of these sources, with review by other individuals, as needed, (e.g., legal counsel). If the input is submitted non-anonymously, the researcher receives a direct response. If the outcome of the review shows a need for ongoing monitoring or education, then the appropriate individuals (e.g., HRPP staff) are asked to contribute their expertise.

The Vice Provost and Dean of Research handles any concerns or complaints related to the Director of Research Compliance.

Ch. 4: Knowledge of Human Research Protection Requirements

4.1 Education of Individuals Responsible for Human Research

Stanford has an education program that contributes to the improvement of the qualifications and expertise of individuals responsible for protecting the rights and welfare of research participants. (AAHRPP Element I.1.E)

Education and training are provided to all individuals involved with the HRPP. The HRPP Policy Manual specifies education requirements for IRB members, IRB staff, and key personnel on the research team (see [Chapter 4.2](#)). The Research Compliance Office (RCO) works with Stanford University schools and departments, the VAPAHCS, and other institutions, to offer comprehensive education to the Stanford research community.

Education is offered in many areas of research, including ethical standards, related both to research and to professional conduct, Stanford policies and procedures, and applicable federal, state, and local laws. The foundation of ethical training at Stanford is the [Belmont Report](#), which is made available at training sessions and on the Human Subjects Research website.

Research Compliance Office (RCO) Staff

The RCO has full time staff dedicated to developing and providing education for IRB members, IRB staff, and the research community regarding human research protections.

Evaluation of Qualifications

In addition to receiving training on human subject research protections (described in [Chapter 4.2](#)), IRB members and IRB staff are reviewed periodically to evaluate their understanding of the HRPP (ethical principles, policies and procedures, and regulations).

IRB staff qualifications are reviewed during the hiring process and annually or as needed to ensure a high level of commitment to the HRPP.

IRB member qualifications are reviewed by the HRPP Associate Director during the recruitment process, and IRB members are formally appointed by the Vice Provost and Dean of Research. IRB members ([Evaluation of IRB Members](#) [EVA-1] , including IRB Chairs ([Evaluation of IRB Chairs](#) [EVA-2]), are evaluated yearly to ensure that their service on the IRB contributes to the ethical and regulatory review of research at Stanford. Members are re-appointed based on these evaluations. Investigators at Stanford are evaluated according to individual institution, school, and department policies.

The Continuous Quality Improvement (CQI) program (described in [Chapter 3.13](#)) evaluates the effectiveness of the education provided. Results of the CQI evaluations are used to adjust the content of educational materials, improve delivery methods, identify appropriate audiences, and to communicate with the other components of the HRPP about updating their education and training.

Contributing to the Improvement of Expertise

New IRB members and IRB staff receive orientation to the Stanford HRPP. All IRB members and IRB staff receive regular, ongoing training at convened meetings and continuing education. Opportunities for continuing education in human research protections are announced on a regular basis. IRB member and IRB staff attendance is encouraged at regulatory and professional meetings and conferences both locally and nationally, and for web broadcasts and seminars at Stanford and in the greater community. Additionally, the RCO supports and encourages professional certification for qualified IRB staff.

Before IRB members can review protocols according to expedited review procedures, they must meet additional training and participation requirements. Members who review according to the expedited procedure are appointed by an IRB Chair. In addition, the RCO provides specific training tailored to the review of certain protocol types, e.g., protocols involving stem cells or gene transfer materials. IRB members' expertise is considered when assigning primary reviewers (see [Chapter 7](#)).

Educational Materials and Resources

The Stanford research community, IRB members, IRB staff and other individuals responsible for the protection of human research participants have access to a wealth of educational material, available online and in printed format, or offered as courses or workshops. They include, among others:

- The Human Subjects Research [website](#), with links to the Stanford [HRPP Policy Manual](#), instructional information, FAQs, educational material, document templates, forms, and guidance
- Access to required training through the interactive online Collaborative Institutional Training Initiative ([CITI](#)) Course: The Protection of Human Research Subjects.
- Regular ad hoc communications from the RCO
- The Office of the Vice Provost and Dean of Research [website](#)
- The eProtocol electronic protocol submission system, providing instructional text and explanation as part of the application
- eProtocol training
- The Stanford University Research Policy Handbook, in particular, RPH 5.1 [Human Research Protection Program](#)
- [PI-ship Handbook](#) from the Office of the Vice Provost and Dean of Research
- [Spectrum Education](#) provides learning and development opportunities to Stanford faculty, staff, students, and scholars in all areas of clinical and translational research.
- [HIPAA Training](#)

- Local VA researcher training in [VHA Directive 1200.05](#)

Additional education is provided through classes, training courses, workshops, and seminars offered by the RCO and other [HRPP component organizations](#).

Education Planning

Senior HRPP staff members meet regularly to discuss the education provided to IRB staff, IRB members, and investigators. They incorporate input received from IRB members, IRB staff and investigators, and from CQI monitoring and evaluation activities. Trends in research at Stanford are considered, and new federal, state, or local regulations (or published guidance) are integrated. Compliance activities (e.g., internal and external audits) also provide input.

4.2 Required Training in Human Research Protections

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

Completion of human subject training by all staff working on a research project (all investigators and other study personnel, including all persons who are responsible for the design, conduct, data analysis or reporting) is one of the requirements for protocol approval by the IRB. Protocol Directors, as part of the protocol submission process, acknowledge their obligation to protect the rights and welfare of research participants. See [Protocol Application](#) “Obligations” section.

Stanford provides access to the required training through an interactive online tutorial - CITI ([Collaborative IRB Training Initiative](#)) Course in The Protection of Human Research Subjects. CITI offers a basic (initial) course and then a refresher course which must be taken every three years. The required training has been customized for different learner groups (medical and nonmedical investigators, IRB members, IRB staff, and Institutional Officials).

At the completion of the required modules, the learner can download, save, and print a certificate of completion from the CITI website. Individual investigators must maintain their own records. It is the responsibility of the Protocol Director to ensure completion of the required training by all study personnel, including all persons who are responsible for the design, conduct, data analysis or reporting, and to have all certificates of completion available for inspection.

Training records of IRB Staff, IRB Members and Institutional Officials are maintained in the RCO.

RCO and IRB Staff Required Training

Training	IRB Staff, CQI Staff, RCO Sr. Management	Office Support, IT Personnel
RCO orientation for new staff	Required	Required
HRPP Orientation for new staff	Required	As needed
Human Subjects Tutorial (CITI)	Required	n/a
HIPAA training	Required	Required
Continuing HRPP education	Required	As needed

- **IRB Staff** = IRB Managers, IRB Coordination Managers, and their supervisors.
- **CQI Staff** = HRPP education and training staff, compliance staff, records and documentation staff, and their supervisors

For newly hired RCO staff involved in the HRPP:

- **HRPP Orientation** is a three-month process managed by the IRB Education staff.
- **CITI training** must be completed within 30 days of employment in RCO and must be renewed every three years.
- **HIPAA training** must be completed before handling Protected Health Information (PHI) or within 30 days of employment at Stanford and must be renewed according to institution requirements. (Administrative Guide [1.6.2](#))

See Stanford University general policies ([Administrative Guides](#)) regarding Employee Training.

IRB Members Required Training

Training	Medical IRB Members and Chairs	Nonmedical IRB Members and Chairs	Ex-Officio IRB Members
HRPP orientation for new members	Required	Required	If needed
Human Subjects Tutorial (CITI)	Required	Required	Required
HIPAA training	Required	Required	Required
Continuing HRPP education	Required	Required	Required

Institutional Officials Required Training

Institutional officials at Stanford University and the VAPAHCS must take CITI training.

Investigator Required Training

Stanford requires that Protocol Directors and other key personnel involved in the design or conduct of a project, including those projects that may be deemed exempt under 45 CFR 46, provide evidence of training and qualifications by submitting relevant documentation as requested by the sponsor, IRB, or regulatory authorities. See [Chapter 15.1](#).

The IRB-required training of investigators and other key personnel must be completed prior to IRB protocol approval.

Key personnel: all investigators and other study personnel, including all persons who are responsible for the design, conduct, data analysis or reporting of research that involves human subjects. Key personnel may include faculty, staff, students, or visiting or contract personnel, persons who obtain informed consent, administer surveys, or collect private or personal information from individuals.

The IRB training requirement applies to individuals working under the auspices of Stanford University, whether at Stanford facilities or at another location, and regardless of their institutional affiliation or source of funding. In the event that individuals from other institutions (“third-party” or contract employees) conduct research under the auspices of Stanford, they must complete human subjects protections training, but may do so at their home institution. A letter, certificate, or email notification by a representative from their home institution will satisfy this requirement. Similarly, new Stanford employees can meet the training requirement if they have completed human subjects protections training at their prior institution within the applicable timeframe. Third-party individuals and new Stanford employees may also take the Stanford CITI modules, if desired. All IRB-required training completion records must be maintained by the Stanford Protocol Director.

Researchers and Research Staff recruit participants in a fair and equitable manner. (AAHRPP Element III.1.E)

Training	SU, SHC, and LPCH Investigators	VA Investigators
Human Subjects Tutorial (CITI)	Required Group 7 (medical) Group 2 (nonmedical)	VA Research Administration determines which modules should be taken
Stanford HIPAA training	Required	Required

- Examples of investigator training required or recommended per other Stanford, non-IRB policies, typically prior to engaging in research are listed below. Refer to individual entities and departments for more information.
- **Data Security and Secure Computing** ([Information Security Office](#)):

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- STARS training: [Computer Security Awareness \(ISO-0001\)](#)
- [Computer Security Risks and Mitigations](#)
- **GCP training:** available through CITI for all researchers
- **Managing Cost Issues** (Office of Research Administration)
- **Sponsor-Investigator** Training (Spectrum, CCTO)
- **ABCs of Research** (Office of Research Administration)
- **Ethics** training courses and resources (Stanford Center for Biomedical Ethics, or Program for Ethics in Society)
- **Stewardship and Compliance** for PIs (Office of the Vice Provost and Dean of Research)
- **PI Health and Safety** Training (School of Medicine)
- **Sponsored Projects Administration** Overview (Office of Research Administration)
- **Environmental Health and Safety** training ([Environmental Health and Safety](#))
- **VA:** [VHA Directive 1200.05](#)

Individual investigators maintain their own training records for CITI, HIPAA, and any other required training.

The IRB staff is a resource for any questions regarding HRPP education for the research community.

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Ch. 5: Investigational or Unlicensed Test Articles – Research with Drugs, Devices or Biologics

When research involves investigational or unlicensed test articles, Stanford confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.
(AAHRPP Element I.7.A)

This chapter outlines policy for

- research using investigational drugs, devices, or biologics (in this chapter, the term investigational means unapproved drugs, unapproved devices or devices not cleared to market, or unlicensed biologics)
- research with FDA-approved drugs, approved/cleared devices, or licensed biologics (sometimes called “commercially available”)
- sponsor-investigator research
- radiation devices and radioactive materials
- handling (inventory control and storage) of investigational drugs, devices, or biologics
- emergency, humanitarian, or compassionate use of investigational drugs, devices, or biologics

FDA regulates clinical investigations (research) “that support applications for research or marketing permits for products regulated by the Food and Drug Administration, including foods, dietary supplements that bear a nutrient content claim or a health claim, infant formulas, food and color additives, drugs for human use, medical devices for human use, biological products for human use, and electronic products.” (See [21 CFR 56.101](#))

All such investigations must be conducted in accordance with FDA requirements for informed consent and IRB review, regardless of funding source or sponsor.

Required Study Registration

- **ClinicalTrials.gov:** [Applicable clinical trials](#), as defined in 42CFR 11.22(b)), and NIH-funded clinical trials, as defined by [NIH Policy](#), must be registered on *ClinicalTrials.gov*; clinical trial information must be submitted for inclusion in the clinical trial registry databank (Public Health Service Act, section 402(j) and a corresponding statement added to the consent form (see [General Requirements for Informed Consent](#) GUI-C41.) Spectrum also has [clinical trials.gov support](#) for Stanford Investigators. The Stanford School of Medicine requires registration of all clinical trials conducted at Stanford and affiliated facilities in a single, comprehensive and publicly accessible database administered by [Spectrum](#), the [Stanford Clinical Trials Web Site](#).

The FDA web page [Comparison of FDA and HHS Human Subject Protection Regulations](#) outlines differences between FDA regulations and OHRP [45 CFR 46](#) regulations for the protection of human subjects. Where regulations differ, the IRB applies the stricter one.

5.1 Research with Test Articles

When research involves investigational or unlicensed test articles, Stanford confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (AAHRPP Element I.7.A)

Research with FDA-regulated test articles may commence only after the IRB has approved the protocol and:

- receives documentation that the research will be conducted under an applicable Investigational New Drug Application (IND) or Investigational Device Exemption (IDE); The IND goes into effect generally 30 days after the FDA assigns the IND, unless the sponsor receives earlier notice from the FDA; or
- formally determines and documents that the proposed use of any investigational device satisfies the FDA criteria for non-significant risk devices; or
- formally determines that satisfactory justification has been provided by the investigator as to why an IND or IDE is not required.

The IRB collaborates with Spectrum, CCTO and the Office of the Vice Provost and Dean of Research to support Stanford clinical investigators who conduct FDA-regulated research.

See:

- [Medical Reviewer Checklist Section C \[CHK-3\]](#)

Definitions

Biologic: A biological or related product, regulated by the FDA, including blood, vaccines, allergenics, tissues, and cellular and gene therapies. Biologics, in contrast to drugs that are chemically synthesized, are derived from living sources (such as humans, animals, and microorganisms). Studies of unlicensed biologics are regulated according to the IND regulations, except in some cases when the biologic is in a combination product with a medical device. FDA regulates biologics general use and licensing under [21CFR 600](#) and [601](#). ([42 U.S.C 262](#) of the Public Health Service Act.)

Clinical investigation: 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 under section 505(i) or 520(g) of the [Federal Food, Drug and Cosmetic Act](#) (FD&C Act), or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of

which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that must meet the provisions of part 58, regarding nonclinical laboratory studies. The terms research, clinical research, clinical study, study, and clinical investigation are deemed to be synonymous for purposes of this part. (See [21 CFR 56.102](#))

Combination product: A product containing a combination of a drug, a device, or a biological product. Studies of combination products are regulated according to the IND or IDE regulations, depending on the components of the product. The FDA determines which of its organizational components has primary jurisdiction for the premarket review and regulation of products that are comprised of any combination of a drug, device, and/or biological. (See [21 CFR 3.2\(e\)](#))

Human subject: An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy individual or a patient. (See [21 CFR 56.102](#))

Off-Label: Use of an approved drug, an approved or cleared device, or a licensed biologic for an indication not in the approved labeling. Most research involving off-label uses requires IND or IDE applications. See FDA ["Off-Label" and Investigational Use of Marketed Drugs, Biologics and Medical Devices](#).

Test article: Any drug for human use, biological product for human use, medical device for human use, human food additive, color additive, electronic product, or any other article subject to regulation under the act or under sections 351 or 354-360F of the Public Health Service Act. (See [21 CFR 56.102](#))

5.2 Research with Drugs

When research involves investigational or unlicensed test articles, Stanford confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (AAHRPP Element I.7.A)

Clinical investigations of drugs are subject to the Investigational New Drug Application (IND) regulations, [21 CFR 312](#).

An investigational new drug application (IND) is synonymous with “Notice of Claimed Investigational Exemption for a New Drug.” An investigational drug must have an IND before it can be shipped, unless one of the exemptions outlined in [21 CFR 312.2](#) is met.

Applications for research on the use of a drug, unless that research is exempt from the IND regulations, must be accompanied by documentation from the FDA that includes a valid IND number. The IND number must either match the number on the sponsor protocol with the

same title as the proposed research or be listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IND numbers may not be validated with an Investigator Brochure (which may serve multiple INDs).

As stated in [21 CFR 312.2\(b\)](#), clinical investigation of a drug is exempt from the IND regulations if the drug is lawfully marketed in the United States and all of the following are true:

- (i) The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- (ii) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
- (iii) The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;
- (iv) The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50; and
- (v) The investigation is conducted in compliance with the requirements of [312.8](#) (Promotion and charging for investigational drugs).

Additionally, a clinical investigation involving use of a placebo is exempt from the requirements of [21 CFR 312](#) if the investigation does not otherwise require submission of an IND. Clinical investigations that are exempt from IND regulations still require IRB review and approval.

Even when there is no immediate intent to change product labeling or advertising, investigators who are planning rigorous, carefully controlled clinical investigations of off-label uses of approved drugs or biologics should contact the FDA regarding obtaining an IND before submitting a protocol to the IRB.

See the FDA guidance for FDA's current thinking on exemptions from IND regulations for oncology combination protocols. See the FDA guidance [IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products](#).

Studies involving potentially addicting drugs have additional informed consent requirements. See Research Policy Handbook RPH 5.6 [Guidelines for Studies Involving Human Volunteers Receiving Potentially Addicting Drugs](#).

VA Research

For clinical investigations of a drug at the VA, investigators must provide documentation and information to the VA Pharmacy Service or Research Service Investigational Pharmacy as specified in and [VHA Handbook 1108.04](#).

5.3 Research with Devices

When research involves investigational or unlicensed test articles, Stanford confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (AAHRPP Element I.7.A)

Clinical investigations of devices are subject to the Investigational Device Exemptions (IDE) regulations, [21 CFR 812](#).

An approved investigational device exemption (IDE) permits a device that is not approved (via premarket authorization, PMA) or cleared to market (via 510(k)) by the FDA to be shipped to conduct clinical investigations of that device. Significant risk investigational devices must have an IDE issued by FDA before they can be shipped. Nonsignificant risk devices are considered to have an approved IDE when the IRB agrees with the sponsor that the device meets the criteria for a nonsignificant risk device.

Research with devices falls into three categories:

- Investigations of significant risk devices to determine safety and effectiveness of the device
- Investigations of nonsignificant risk devices to determine safety and effectiveness of the device
- Investigations exempted from the IDE regulations

See:

- [Significant Risk \(SR\) and Nonsignificant Risk \(NSR\) Medical Device Studies](#) [GUI-7m],
- [Frequently Asked Questions Medical Devices](#) [FDA],
- [Significant Risk and Nonsignificant Risk Medical Device Studies](#) [FDA]

Studies that include medical device use in an incidental way, where the device or the use of the device is not the focus of the research, are generally not considered to be FDA-regulated research or subject to 21 CFR 812, and in some instances are eligible for IRB review according to the expedited procedure.

Significant Risk Device Research

Applications for research on the use of a significant risk device must be accompanied by documentation from the FDA that includes a valid IDE number. The IDE number must either match the number on the sponsor protocol with the same title as the proposed research, be

listed on communication from the sponsor specific to the proposed research, or on communication with the FDA. IDE numbers may not be validated with a device manual (which may serve multiple IDEs).

Nonsignificant Risk Device Research

When research is conducted to determine the safety or effectiveness of a device, the organization confirms that the device fulfills the requirements for an abbreviated IDE (21 CFR 812.2(b)(1)):

- The device is not a banned device;
- The sponsor labels the device in accordance with 21 CFR 812.5;
- The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device, and maintains such approval;
- The sponsor ensures that each investigator participating in an investigation of the device obtains from each subject under the investigator's care, consent under 21 CFR 50 and documents it, unless documentation is waived;
- The sponsor complies with the requirements of 21 CFR 812.46 with respect to monitoring investigations;
- The sponsor maintains the records required under 21 CFR 812.140(b) (4) and (5) and makes the reports required under 21 CFR 812.150(b) (1) through (3) and (5) through (10);
- The sponsor ensures that participating investigators maintain the records required by 21 CFR 812.140(a)(3)(i) and make the reports required under 21 CFR 812.150(a) (1), (2), (5), and (7); and
- The sponsor complies with the prohibitions in 21 CFR 812.7 against promotion and other practices.

If the investigator applies to the IRB for a nonsignificant risk determination for a device study, but the IRB determines that the device is significant risk, the IRB shall notify the investigator and the sponsor, if appropriate.

Exempt Device Research

Clinical investigations that are exempt from IDE regulations still require IRB review and approval. An investigation of a medical device in human subjects research that is exempt from the IDE regulations must fall into one of the following categories (Criteria in [21 CFR 812.2\(c\)](#)):

- A device legally marketed in the US that is used or investigated in accordance with the indications in the FDA-approved labeling.

- A diagnostic device (that is, an in vitro diagnostic device) if the testing:
 - Is noninvasive
 - Does not require an invasive sampling procedure that presents significant risk,
 - Does not by design or intention introduce energy into a subject, and
 - Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- A custom device as defined in 21 CFR 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.
- A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.

In Vitro Diagnostic Device Research

In vitro diagnostic (IVD) device investigations may be exempt from the IDE requirements of 21 CFR 812 if the devices are properly labeled and meet the criteria set forth in 21 CFR 812.2(c)(3). However, such studies are still subject to the FDA regulations and IRB review requirements if the research is to support an application for research or marketing of the device (see 21 CFR 50.1). This is true regardless of whether the samples to be used are individually identifiable or not. The FDA regulations define a subject to include a human on whose specimens an investigational device is used (21 CFR 812.3(p)). Thus, an IVD study to support a premarket submission to the FDA is considered a human subject investigation and is subject to IRB review under 21 CFR parts 50 and 56. IVD research may be eligible for expedited review and without informed consent if the study involves leftover human specimens and as long as subject privacy is protected by using only specimens that are not individually identifiable, when appropriate.

In addition to the above, FDA [Guidance on Informed Consent for In Vitro Diagnostic Device Studies Using Leftover Human Specimens that are Not Individually Identifiable](#) makes clear that

IRB review is one of several criteria for IVD studies using leftover specimens that are not individually identifiable.

5.4 Radiology Devices and Radioactive Materials

When research involves investigational or unlicensed test articles, Stanford confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.
(AAHRPP Element I.7.A)

The FDA regulates radiology devices and radioactive materials used in research. Oversight at Stanford is handled by the Administrative Panel on Radiological Safety (APRS) which is chartered as a Radioactive Drug Research Committee (RDRC) by the FDA under 21 CFR 361.1. Most research involving radiation is covered by an IND or an IDE and must be reviewed and approved by the IRB.

As defined in 21 CFR 361.1 the APRS has no oversight responsibility or authority over an investigation carried out under an IND exemption. This authority is retained by the FDA. If a radiopharmaceutical cannot be classified as “generally recognized as safe and effective,” (see [Guidance for use of Radiology Devices and Radioactive Materials in Research Protocols](#)) the APRS may not review and approve the research, and an IND may be needed. Environmental Health and Safety, Office of Health Physics provides information regarding which studies do not need IRB approval and can be reviewed by APRS only. See the EH&S [Health Physics Program](#) website.

The [Protocol Application](#) includes the necessary radiological safety questions which are reviewed by both the IRB and a member(s) of APRS. In addition, Health Physics provides assistance for protocol directors designing studies with radiation. See EH&S [Guidance for Preparing Research Proposals Involving Diagnostic Use of Ionizing Radiation in Human Use Research](#).

5.5 Research with Biologics

When research involves investigational or unlicensed test articles, Stanford confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval.
(AAHRPP Element I.7.A)

Clinical investigations of biologics are regulated in the same way as clinical investigations for drugs, and require an IND, unless the biologic is part of a combination product that the FDA has assigned for premarket approval to the Center for Devices and Radiological Health (CDRH). In such cases, the biologic/device combination product would require an IDE prior to research approval by the IRB.

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Generally, protocols using biological agents or recombinant DNA vectors are reviewed by IRBs 1 and 3. The Research Policy Handbook RPH 7.8 [Biohazardous Agents and Recombinant DNA](#) provides more information about research with biohazardous agents and human subjects.

5.6 Sponsor-Investigator Research

When research involves investigational or unlicensed test articles, Stanford confirms that the test articles have appropriate regulatory approval or meet exemptions for such approval. (AAHRPP Element I.7.A)

Stanford has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements. (AAHRPP Element I.7.B)

In reviewing research involving test articles, the IRB determines if a Stanford investigator holds his or her own IND or IDE. If so, the IRB confirms that the investigator understands his or her additional responsibilities as the sponsor of the research, including reporting requirements to the FDA.

Sponsor-investigators who submit protocols to the IRB involving FDA test articles must include all supporting FDA documentation for their IND or IDE and any Stanford required approvals for applying for an IND or IDE. Additionally, if the IND or IDE product will be manufactured at Stanford, the Protocol Director must submit written documentation that:

- The product preparation and manufacture meet the standards for current Good Manufacturing Practice (GMP), or any modification to those standards approved by the FDA in issuing the IND or IDE.
- The GMP plan has been approved by the applicable Stanford official, appointed by the Sr. Assoc. Dean of Research in the School of Medicine.
- The GMP plan has been reviewed and accepted by Risk Management if the sponsor-investigator is a Stanford investigator.

The IND or IDE product must be stored, secured, dispensed, and documented in accordance with the policies of the Stanford institution in which it will be used, i.e., SHC/LPCH (see Section 5.6, Internal Handling of Test Articles), or the Veterans Affairs Palo Alto Health Care System.

In coordination with the Research Compliance Office, education covering these responsibilities is provided by: (i) Spectrum, the unit in the Stanford University School of Medicine providing administrative support for clinical trials, to sponsor-investigators who are faculty and conducting clinical trials at SHC and LPCH, and (ii) the Palo Alto Veterans Affairs Health Care System for its employees who are sponsor-investigators.

Prior to approving a protocol that involves a sponsor-investigator, the IRB must be satisfied that the sponsor-investigator is knowledgeable about his/her responsibilities and has adequate policies and procedures in place to comply with the FDA regulatory requirements. The IRB may rely on feedback from the Stanford entity providing the education in its determination of proficiency but may also contact or site visit the sponsor-investigator as deemed necessary. A compliance review, designed to evaluate compliance with the FDA regulatory requirements, must be conducted on at least an annual basis as a condition for renewal of the protocol by the IRB.

Investigator-held INDs

A sponsor-investigator for an IND protocol must follow the FDA regulations in [21 CFR 312](#) applicable to sponsor responsibilities.

See [Sponsor-Investigator Research when the Stanford investigator holds the IND](#) [GUI-3m].

Investigator-held IDEs - Significant Risk Devices

A sponsor-investigator for an IDE protocol must follow the FDA regulations in [21 CFR 812](#).

See [Sponsor-Investigator Research when the Stanford investigator holds the IDE](#) [GUI-5m].

Nonsignificant Risk Device Studies when Investigator Acts as Sponsor

Investigators studying nonsignificant devices, regulated by the abbreviated IDE regulations, have abbreviated sponsor responsibilities when there is no industry sponsor. See guidances:

- [Significant Risk \(SR\) and Nonsignificant Risk \(NSR\) Medical Device Studies](#) [GUI-7m],
- [Sponsor-Investigator Research Requirements \(when a Stanford investigator is the sponsor on a non-significant risk device study\)](#) [GUI-41m].

5.7 Internal Handling of Test Articles

Stanford has and follows written policies and procedures to ensure that the handling of investigational or unlicensed test articles conforms to legal and regulatory requirements.
(AAHRPP Element I.7.B)

These policies and procedures are found in the Stanford Hospital and Clinics (SHC) Administrative Guide and in the Lucile Packard Children's Hospital (LPCH) Formulary.

The policies for SHC and for LPCH outline the standards relating to drugs and devices for pharmacy practices, inventory control and documentation. See:

- SHC policy "[Investigational Drugs and Biologics](#)"
- LPCH policy "[Investigational Drugs and Biologics](#)"
- SHC and LPCH policy "[Investigational New Devices](#)"

For clinical investigations, Stanford University promotes researchers' adherence to ICH guidelines as presented by the FDA in the form of the [Consolidated Guidance for Good Clinical Practice](#) (GCP).

Veterans Affairs (VA) Requirements

VA policy (M-3, Part 1, Chapter 9) requires that all research comply with the VA human subject regulations, as well as with all applicable regulations and requirements regarding storage and security procedures for investigational agents.

For clinical investigations of a drug at the VA, investigators must provide documentation and information to the VA Pharmacy Service or Research Service Investigational Pharmacy as specified in [VHA Handbook 1108.04](#).

5.8 Expanded Access to Investigational Drugs and Devices for Treatment Use

Expanded access to investigational drugs and devices requires prior IRB review and approval (with the exception of Emergency Use, [Chapter 5.9](#)).

5.8.1 Drugs

Definitions

Expanded access: Use of investigational new drugs and approved drugs where availability is limited by a risk evaluation and mitigation strategy (REMS) when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The aim of this subpart is to facilitate the availability of such drugs to patients with serious diseases or conditions when there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the patient's disease or condition. [[21 CFR 312.300 \(Subpart I\)](#)]

Expanded Access Programs (EAPs): The FDA uses this term to refer to the various types of allowable expanded access use.

Immediately life-threatening disease or condition: A stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.

Serious disease or condition: A disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one.

There are 3 categories of expanded access program (EAP) for investigational drugs:

- (i) Single patients, including for emergency use ([Chapter 5.9](#)), ([21 CFR 312.310](#)).
- (ii) Intermediate-size patient populations ([21 CFR 312.315](#))
- (iii) Treatment IND or “treatment protocol” for widespread treatment use ([21 CFR 312.320](#))

See [Expanded Access](#) [GUI-19m].

5.8.2 Devices

The FDA may make an unapproved device available under several mechanisms:

- [Emergency Use](#): See [Chapter 5.9](#).
- [Compassionate Use](#) (or Single Patient/Small Group Access)
- [Treatment Use](#) (Larger Group/More Widespread Use)
- [Expanded Access](#)

See [Expanded Access](#) [GUI-19m].

5.9 Emergency Use of a Test Article

Stanford has and follows written policies and procedures for compliance with legal and regulatory requirements governing emergency use of an investigational or unlicensed test article. (AAHRPP Element I.7.C)

Emergency Use: Use of a test article on a human participant in a life-threatening situation in which no standard acceptable treatment is available, and in which there is not sufficient time to obtain IRB approval ([21 CFR 56.102\(d\)](#)).

Specific additional requirements apply; see [Emergency Use of a Test Article](#) [GUI-6].

5.10 Humanitarian Use Device (HUD); Orphan Drugs

Humanitarian Use Device (HUD)

A Humanitarian Use Device (HUD) is a device intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year. The regulations under [21 CFR 814 \(Subpart H\)](#) were designed to promote the development of devices for diseases affecting these populations.

See [Humanitarian Use Device](#) [GUI-36m].

Orphan Drugs

The [Orphan Drug Designation program](#) provides orphan status to drugs and biologics which are defined as those intended for the safe and effective treatment, diagnosis or prevention of rare

diseases/disorders that affect fewer than 200,000 people in the U.S. These drugs are not expected to recover the costs of developing and marketing as treatment drugs.

5.11 Planned Emergency Research

Planned emergency research: Planned research in life-threatening emergent situations where obtaining prospective informed consent has been waived ([21 CFR 50.24](#)).

- The research plan must be approved in advance by the FDA and IRB. The IRB will follow the HHS and FDA harmonized criteria for review set forth in [21 CFR 50.24](#) and in the flow-chart in [FDA’S Guidance for Institutional Review Boards, Clinical Investigators, and Sponsors Exception from Informed Consent Requirements for Emergency Research, Appendix C](#). The research plan must also be disclosed to the communities where the research will be conducted and from where participants will be drawn, including presentation of the risks and expected benefits of the research. An independent data monitoring committee (DMC) must be established to exercise oversight of the research. When the research is not regulated by the FDA, advance notice of these protocols will be provided to the Office for Human Research Protections pursuant to federal regulation 45 CFR 46.101(i). PDs who wish to conduct planned emergency research should consult with IRB staff prior to submission of the protocol to the IRB.
- Planned emergency research is usually not eligible for emergency use approvals.

VA Research

Planned emergency research cannot be conducted by the VA.

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Ch. 6: Structure and Composition of the IRB

6.1 Scope of IRB Authority

The IRB derives its authority from both federal regulatory and institutional sources. Institutional authority is conveyed by the Vice Provost and Dean of Research through approval of this chapter and other chapters of the HRPP Policy Manual. Additionally, the Vice Provost and Dean of Research issues a direct, written delegation of authority under an institutional Charge to IRB members upon their appointment to the IRB (see Charge to IRB members ([medical](#) and [nonmedical](#))). The Vice Provost and Dean of Research in turn has the authority [delegated](#) to him or her from the President of Stanford University (President). On a day-to-day basis, the IRB reports to the Vice Provost and Dean of Research, through the RCO Director. However, the IRB Chair, an IRB member, or the convened IRB may refer a matter directly to the President on those extraordinary occasions when it may be deemed warranted.

The IRB has the statutory and institutional authority to take any action necessary to protect the rights and welfare of human research participants involved in research. For example, the IRB assesses suspected or alleged protocol deviations, participant complaints, or violations of external regulations or Stanford policies. The IRB has the authority to suspend or terminate the enrollment or ongoing involvement of research participants in research as it determines necessary for the protection of those participants. The IRB also has the authority to observe or monitor any human research to whatever extent it considers necessary to protect research participants. ([45 CFR 46.109](#), [46.112](#), [46.113](#), and [VHA Directive 1200.05](#)). The IRB Staff has the authority for determining whether activities constitute human subjects research and in making exempt determinations.

Upon request, the IRB shall review and comment on proposed external regulations dealing with human research. When appropriate, the IRB will formulate draft policies and procedures for approval by the appropriate Stanford bodies and promulgation by the Vice Provost and Dean of Research.

Decisions of the IRB

IRB approval is always necessary before a research project involving research participants may begin. An IRB decision to not approve a human research project, or require modifications as a condition for approval, cannot be overturned by any Stanford official or Stanford committee.

The IRB must provide the investigator with a written statement of the reasons for not approving proposed research and must give the investigator an opportunity to respond in person or in writing. The IRB must carefully and fairly evaluate the investigator's response in reaching a final determination.

If an investigator has concerns with respect to procedures or decisions of the IRB, the investigator may discuss his/her concerns with the Vice Provost and Dean of Research with the understanding that neither the Vice Provost and Dean of Research, the Provost, nor any other

Stanford official or committee may approve a protocol that has not been approved by the decision of one of the Panels, nor apply undue pressure on the Panel to reverse a decision.

At the time an investigator seeks to discuss his or her concerns with the Vice Provost and Dean of Research, those concern(s) must be in writing, and the Vice Provost and Dean of Research will use his or her sole discretion to determine the process for responding to the concern, included but not limited to:

- Notifying the IRB of the concern and requesting a response and relevant information from its records
- Appointing a factfinder to review the matter and report back to the Vice Provost and Dean of Research
- Seeking assistance from consultants or internal administrative units such as the Office of Audit, Compliance, Risk and Privacy or Office of the General Counsel.

However, all such reviews are subject to the fundamental principle that no one at Stanford can approve a human subjects protocol that has not been approved by an IRB Panel, nor apply pressure on the Panel to reverse a decision. Thus, all policies clearly state that no other review or person at Stanford can overturn the decision of an IRB Panel.

Reporting Obligations within Stanford

The IRB is administered by the RCO and reports to the Office of the Vice Provost and Dean of Research. The Vice Provost and Dean of Research is the institutional official responsible for assuring compliance with Stanford policies and external regulations on the use of human research participants and is the head of the Stanford HRPP. IRB Chairs prepare annual reports to the Vice Provost and Dean of Research, summarizing the nature and volume of the IRB activities and resources needed for the new academic year.

Responsibilities to Regulatory Agencies

The IRB must comply with the requirements of all relevant federal regulatory and compliance enforcement agencies or offices, including OHRP and FDA, as well as relevant agencies of the State of California.

6.2 Relationships between the IRB and Others

The IRB is required at times to participate with other programs or research compliance committees at Stanford that also have responsibility for the ethical oversight of research within the HRPP. In some cases, the approval of another Stanford body may be required prior to or in addition to IRB review. Such cases include:

Radiological Safety: If a study involves any radioisotopes or radiation-producing machines, the Radiation Safety Committee must certify that it has reviewed a protocol using radioisotopes or radiation machines and recommends it for approval. Without this approval, a study which

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employs these modalities will either be tabled to a future convened meeting or will be approved contingent on Radiation Safety Committee recommendation for approval. If a modification involves review by Radiation Safety, the IRB will hold its approval until Radiation Safety forwards its approval to the IRB. Radiation Safety is given access to the protocol information by the IRB.

Protocols involving biosafety materials and requiring review by the Biosafety Panel must be reviewed by this Panel and receive an approval letter in addition to review by the IRB. A new protocol generally will not be presented at an IRB convened meeting until the Biosafety Panel has approved it. If a modification or continuing review involves review by Biosafety, the IRB may hold its approval until Biosafety forwards its approval to the IRB. The HRPP Associate Director, and the Senior IRB Manager are ex-officio members of the Biosafety Panel. A senior member of the IRB staff attends the Biosafety Panel meetings and receives communications directly from the Panel regarding submitted protocols. The Biosafety Officer and Biosafety Specialist (from the Environmental Health & Safety department) are ex officio members of the medical IRBs and IRB/SCRO and attend medical IRB and IRB/SCRO Panel meetings.

Investigator Conflict of Interest disclosures: All investigator conflicting interest is managed via the Conflict of Interest Review Program (COIRP) and its associated Institutional Conflict of Interest Committee (ICOIC). The IRB will not approve a protocol until any disclosed COI has been reviewed and resolved by the COIRP/ICOIC, and as appropriate, a plan or strategy to adequately eliminate, mitigate, or manage the conflict has been determined by the COIRP/ICOIC. See [Chapters 3.7](#) and [14.1](#).

Clinical and Translational Research Unit (CTRU): Depending upon the nature of the research, for any human research supported by the [CTRU](#), in addition to IRB approval, CTRU approval must be obtained prior to enrolling participants in the study.

The Stanford Cancer Institute: Protocol review by the Stanford Cancer Center's [Scientific Review Committee](#) (SRC) is conducted in parallel with IRB review. Both IRB and SRC approvals are required to conduct research supported by the Stanford Cancer Institute.

The Veterans Affairs Research and Development (R&D) Committee: Human research involving facilities or personnel of the Department of Veterans Affairs Palo Alto Health Care System (VAPAHCS) must be approved by the IRB prior to being placed on the agenda of the VAPAHCS R&D Committee for review and approval.

Stem Cell Research Oversight: Any human research involving human stem cells must be reviewed by the Stem Cell Research Oversight Panel ([SCRO](#)) as well as the IRB.

See RPH 5.8 [Human Stem Cell Research](#).

Relationships with Industry Sponsors and Other IND or IDE Holders

Unless specifically required by the FDA or requested by the sponsor, the IRB will not routinely provide written notification of IRB decisions to industry sponsors and other holders of INDs or IDEs (Stanford sponsor-investigators excepted). For FDA-regulated research, clinical

investigators generally serve as the link between the IRB and the sponsor and are required to do so by the FDA in compliance with their obligations as clinical investigators. This relationship is agreed to by investigators when they sign FDA Form 1572 (for drug and biologic studies) or an investigator agreement for device studies.

There are occasions when direct communication between the IRB and the sponsor may facilitate resolution of concerns about study procedures or specific wording in an informed consent document. The IRB staff may engage in such direct communication on behalf of the IRB when the IRB Chair or the RCO Director considers it desirable. The clinical investigator will be kept apprised of such communication.

The FDA indicates that direct communication between the sponsor and the IRB may be appropriate when the IRB does not accept a sponsor’s Nonsignificant Risk (NSR) designation of a medical device (21 CFR 812.66). Direct communication between the sponsor and the IRB is required for the waiver of informed consent in planned emergency research relative to (a) the public disclosures required under 21 CFR 50.24(a)(7)(ii),(iii); or (b) disapproval of such a waiver under 21 CFR 50.24(e).

See [Chapter 5.11](#).

6.3 IRB Composition and Membership

The IRB has qualified leadership (e.g., chair and vice chair) and qualified members and staff. Membership and composition of the IRB are periodically reviewed and adjusted as appropriate. (AAHRPP Element II.1.B)

Each IRB has a qualified Chair, members, and staff whose membership and composition is reviewed and adjusted annually by the RCO Director and the Vice Provost and Dean of Research. This review ensures that individual IRB Chairs and members have the knowledge, skills, professional competence, and abilities appropriate to their respective roles and perform their responsibilities in an acceptable manner.

Stanford policy requires that the IRB be constructed of at least 5 members according to DHHS regulations and FDA regulations (45 CFR 46.107 and 21 CFR 56.107). Additionally,

- The IRB shall include a nonscientific IRB member, educated and with experience in unambiguously nonscientific areas (see [Checklist for Determining if IRB Members are Nonscientists](#)), to represent the perspective of research participants. These individuals may not have meaningful scientific or medical training or experience. Health professionals, regardless of discipline, may not be considered nonscientists. At least one nonscientist IRB member must always be present to have a quorum. (See discussion of quorum in [Chapter 6.8](#).)

- The IRB shall include student(s), when nominated by the ASSU Committee on Nominations, who are either upperclassmen or preferably graduate students with previous human research experience.

The VA shall assist the IRB in recruiting VA representatives for IRB membership. VA representation on external IRBs, such as academic IRBs, is optional and at the discretion of the Organizational Official and the external IRB.

- VA representatives to the IRB shall be appointed by the VA Medical Center Director.
- VA Research and Development administration officials including, but not limited to, the Associate Chief of Staff for Research and Development and the Administrative Officer for Research and Development shall be prohibited from serving as voting members of the IRB.
- When VA research involves persons vulnerable to coercion or undue influence, the IRB membership should consider the inclusion of at least one member who is knowledgeable and experienced in this area of the research.

Appointment of Members and Alternates, Length of Service, and Duties

IRB members are nominated from a variety of sources, including previous IRB members, division chiefs, department chairs, compliance administrators, faculty, hospital pharmacy and nursing staff, research laboratories, administrative IRB staff with CIP or equivalent experience, Associated Students of Stanford University (ASSU), and various public groups. Consideration is given to balancing race, gender, expertise, and cultural backgrounds. People with active licensure from various clinical disciplines are sought. A background knowledge of and current familiarity with affiliated institutional concerns (e.g., the VA, LPCH, SHC) helps ensure that the local research context is brought to IRB deliberations. Sensitivity to issues such as community attitudes and international dimensions is valued. Newly identified nominees are contacted by the HRPP Associate Director (or delegate) about their willingness to voluntarily serve on the IRB and their availability for the coming year. When a nominee agrees to serve on the IRB, the RCO Director and Vice Provost and Dean of Research review his or her CV and any relevant correspondence. Stanford has eight IRBs and members can be appointed to one or more of the IRBs depending on their availability and areas of expertise.

Stanford has and follows written policies and procedures to separate competing business interests from ethics review functions. (AAHRPP Element II.1.C)

To avoid any possible conflicting interests or influence on IRB determinations due to competing business interests, individuals who are responsible for development activities (including raising funds) or are in a position to influence programmatic and budgetary decisions may not serve as IRB Members. See [Chapter 6.6.1](#).

After an extensive review of a potential member's education, experience and other characteristics that might add diversity to the IRB, a new IRB member is formally appointed by the Vice Provost and Dean of Research. Members serve one-year renewable terms (from

October 1 to September 30). Members who are VA representatives are appointed by the VA facility Director (the IO) for a period of up to 3 years. They may be re-appointed to new terms of up to 3 years without a lapse in service at the end of each term. After initial appointment to the IRB, members may be asked to serve on a different or additional IRB(s) at the discretion of the HRPP Associate Director. At the conclusion of the IRB year (and interim, if needed), members' contributions are evaluated by the IRB Chair with the IRB manager (See [Chapter 4](#)). If their service is satisfactory, and continued membership is mutually desired, they are eligible for reappointment. All members may be re-appointed at the end of their terms without lapse in service. An IRB member may be removed at the discretion of the Vice Provost and Dean of Research in consultation with the Chair of the Panel and the Director of RCO.

Members are responsible for ensuring that the rights and welfare of research subjects are protected. Members vote to approve, require modifications in, disapprove, or defer research submitted to the IRB. Members are expected to attend IRB meetings on a regular basis, serve as primary reviewers for research within their areas of expertise, and serve as general reviewers on all research. Members may also be asked to participate in subcommittees, audits, and education, as long as there is no conflict of interest with their IRB responsibilities or their other personal or professional roles.

Qualification to Perform Expedited Review

An IRB member may perform protocol review according to the expedited procedure when the IRB Chair, in consultation with the IRB manager, determines that the member is "experienced" with regard to this purpose. There are several ways a member may achieve sufficient experience, including attendance at IRB meetings, targeted education, working with a mentor, independent study, and previous IRB service. See [Chapter 7](#) for more information.

Appointment of IRB Chair, Length of Service, and Duties

IRB Chairs are nominated from a variety of sources, including previous and current IRB members, division chiefs, senior deans, department chairs, and compliance administrators. In addition to the characteristics sought in an IRB member, these individuals possess demonstrated skills in leadership and group process. Typically, they have served on an IRB previously.

IRB Chairs are formally appointed by the Vice Provost and Dean of Research. Chairs serve one-year renewable terms (from October 1 to September 30). At the conclusion of the IRB year (and interim, if needed) the IRB Chairs' contributions are evaluated by the Vice Provost and Dean of Research with the RCO Director (See [Chapter 4](#)). If their service is satisfactory, and their continued service is mutually desired, they are eligible for reappointment. An IRB Chair may be removed at the discretion of the Vice Provost and Dean of Research in consultation with the Director of RCO.

In addition to the responsibilities of IRB membership, the Chair has primary responsibility for conducting IRB meetings and working with staff to ensure effective and efficient operation of

the IRB within all applicable regulatory requirements. The IRB Chair works with IRB members, institutional officials, and investigators to ensure that the rights and welfare of research participants are adequately protected.

Compensation of IRB Members

IRB Chairs' departments receive a percentage of their salaries to offset the time dedicated to IRB duties. IRB members generally do not receive monetary compensation for their service on the IRB. However, it is recognized that service on the IRB requires a significant investment of time for all members.

IRB members who are not otherwise affiliated with Stanford or its collaborating institutions are compensated for their service by the issuance of an honorarium. Compensating unaffiliated members in this way does not create an affiliation or cause a conflict of interest.

Alternate IRB Members

Alternates replace regular IRB members who are unable to attend convened meetings of the IRB. They are required to have similar qualifications and characteristics of expertise and diversity as the regular IRB members (i.e., alternates for scientists are scientists and alternates for non-scientists are also non-scientists) and the primary member for whom each alternate is substituting must be named ([VHA Directive 1200.05](#)). When an alternate substitutes for a regular member, the IRB staff provides the alternate member the same material that the regular member received or would have received.

In some cases, alternate members are able to represent similar specific vulnerable populationsTerms of appointment, length of service, and duties are the same as for regular IRB members. Alternate members must adhere to the same conflict of interest standards and documentation requirements as regular IRB members.

If an alternate member attends a convened meeting at which his or her regular member is in attendance, one of them does not vote.

Ex Officio IRB Members

An ex officio member is designated as an IRB member by virtue of that individual’s office. For example, if the chair of the Administrative Panel on Radiological Safety changes hands, that ex officio IRB membership changes hands accordingly and does not remain with the individual who has left that office. Some ex officio members serve on other Stanford compliance panels and may provide expertise to IRB members. Ex officio members may participate in the IRB deliberations to provide information and expertise as requested by the IRB. Ex officio members are expected to adhere to the same conflict of interest standards and documentation requirements as regular IRB members and alternates. Ex officio members may not vote on any IRB action or determination, and for this reason are sometimes referred to as “non-voting” members.

The medical IRBs accept permanent ex officio representatives from the following areas:

- Office of the Vice Provost and Dean of Research
- Office of the General Counsel
- Biosafety Panel
- Radiological Safety Panel
- Research Management Group
- VAPAHCS Research and Development Office
- Palo Alto Veterans Institute for Research (PAVIR)
- Institutional Animal Care and Use Committee (IACUC/APLAC)

The nonmedical IRB accepts permanent ex officio representatives from the following areas:

- Office of the Vice Provost and Dean of Research
- Office of the General Counsel

The IRB may accept additional permanent ex officio members with the agreement of the IRB Chair and the RCO Director.

Liability Coverage for IRB members

Stanford University provides liability coverage under its insurance programs for IRB members acting in good faith in the performance of their IRB duties. The Stanford University Office of Risk Management provides liability coverage of volunteer individuals, including community IRB members. All Stanford University-related faculty, staff, and students are likewise covered in their capacity as employees and students.

Support of IRB Membership

The IRB has a qualified staff, dedicated to supporting the IRB in its mission to protect human participants in research. The IRB staff teams are reviewed at least annually by the RCO Director and the Vice Provost and Dean of Research to ensure they continue to provide sufficient resources to the IRB. The IRB staff has knowledge, skills, and abilities appropriate to their respective roles. The RCO Director oversees the RCO Deputy Director and the HRPP Associate Director and is responsible for the overall management of the RCO.

For policies on qualifications, education, and periodic evaluation of RCO staff, see [Chapter 4](#).

6.4 Scientific and Scholarly Expertise of IRB Members

Wide-ranging scientific or scholarly expertise among IRB members allows the IRB to review the broad variety of research in which Stanford investigators are engaged. These policies and procedures require IRB members to be knowledgeable about all relevant regulatory requirements, and to strive to remain impartial and objective during protocol review, deliberation, and voting. The IRB includes several members who are particularly knowledgeable about research ethics and the vulnerable research participants included in Stanford research.

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The IRB uses a “primary reviewer” system. The IRB manager, in consultation with the IRB Chair where appropriate, assigns protocols to primary reviewers, based on each individual’s scientific, scholarly, professional, or clinical expertise. Primary reviewers must have the relevant expertise to conduct an in-depth review of the protocols to which they are assigned. If the IRB manager cannot identify a primary reviewer with the appropriate scientific or scholarly expertise, the IRB manager arranges for expert consultation and will not place the protocol on an agenda until appropriate expertise is made available. Primary reviewers are expected to conduct an in-depth review, and it is the responsibility of primary reviewers to notify the IRB Chair or IRB staff should they feel unqualified or unable to do so. In such cases, the IRB Chair will assign primary review responsibilities to another member who is appropriately qualified or obtain consultation from one or more experts outside the IRB (see below).

When the IRB reviews research that involves categories of participants vulnerable to coercion or undue influence, the review process includes one or more individuals who are knowledgeable about or experienced in working with these participants (children, adults unable to consent, students, etc.). The IRB staff reviews each application to determine whether it involves participants vulnerable to coercion or undue influence and considers the participant population when assigning reviewers.

The IRB is constituted to possess and make use of collective knowledge of applicable regulatory and legal requirements; knowledge of professional standards and practices; knowledge of the local research context and research sites, and their capabilities and limitations; knowledge of community standards and attitudes; scientific, scholarly, clinical, and professional expertise; racial, ethnic, and cultural diversity; and representation of participants’ perspectives.

6.5 Obtaining Additional Expertise

The IRB Chair or IRB staff reviews the proposed convened meeting agenda and determines whether the IRB has the required expertise to review upcoming research. If not:

- The IRB Manager, in consultation with the IRB Chair, will invite individuals with competence in the specific areas needed to assist in evaluating issues that require expertise beyond or in addition to that available on the IRB.
- On an as-needed basis, an IRB primary reviewer may invite individuals with competence in special areas to assist in evaluating specific issues.

Reasons for seeking additional or special competence from outside experts may include (but are not limited to) the need for additional scientific, clinical, or scholarly expertise; the need for particular knowledge and understanding about potentially vulnerable populations of subjects; the desire to ensure appropriate consideration of race, gender, language, cultural background, and sensitivity to such issues as community attitudes.

Additional expertise may be obtained through a member of another IRB, or individuals from various Schools and Departments within Stanford University, such as:

- Medicine, Education, Business, and Law
- Office of Research Administration
- Stanford Center for Biomedical Ethics
- Stanford Center for Clinical and Translational Research and Education (Spectrum)
- Various specialty Clinical Departments at the affiliated institutions
- Stanford Cancer Institute

or from:

- VA Palo Alto Health Care System (VAPAHCS), including the VAPAHCS Research and Development Office
- Experts from other institutions
- Representatives of the community
- Representatives of specific subject populations

The IRB Manager or the IRB Chair makes initial contact with a proposed consultant and notifies the consultant of the IRB member [conflict of interest](#) policy (See [Chapter 6.6](#)). When a consultant is used, their expertise and assessment are documented at the time of the protocol discussion and recorded in the IRB minutes. Consultants do not vote. In some cases, a consultant may provide the IRB with a written report of his or her assessment which is kept with the protocol file. The IRB staff can assist in making the consultation arrangements and in obtaining the required conflict of interest documentation.

All consultants, internal or external to Stanford University, must comply with the IRB conflict of interest policy. They are not considered ad hoc IRB members and cannot vote with the IRB.

The [Guidance for Obtaining Additional Expertise](#) [GUI-12] or an Expert Consultant addresses the use of consultants in further detail.

6.6 IRB Member, IRB Staff, and Consultant Conflicting Interest

The IRB has and follows written policies and procedures so that members and consultants do not participate in the review of research protocols or plans in which they have a conflict of interest, except to provide information requested by the IRB. (AAHRPP Element II.1.D)

See 45 CFR 46.107(e); 21 CFR 56.107(e).

[Guidelines for IRB Members on Conflicting Interest](#) [GUI-I5] includes definitions of conflicting interest and outlines procedures for recusal. This policy applies:

- When protocols and reports are first received by members assigned to review
- During discussion and voting in convened meetings
- When consultants are asked to advise the IRB

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This policy applies to all projects reviewed by the IRB, regardless of whether the project is exempt or considered during full, expedited, or continuing review. This policy also applies to reviews of non-compliance reports and unanticipated problems involving risks to participants or others.

IRB intake procedures take into account conflicts of interest when assigning new protocols to an IRB, such as when any IRB member is named in the research protocol or has a spousal relationship with any research personnel.

IRB Member’s Disclosure of a Conflicting Interest

IRB members who realize they have a conflicting interest when they are first assigned a protocol or report for review must notify the IRB staff or IRB Chair immediately so that the protocol can be reassigned.

IRB members review the draft Agenda List before a convened meeting with the issue of conflicts in mind. Any conflicting interest for protocols to be voted on must be reported to the IRB Chair or RCO Director before the meeting whenever possible.

The IRB Chair begins each meeting with a reminder that proceedings are confidential. This is followed by a reminder of the requirement that each member must disclose any conflicting interest and recuse him or herself from the discussion of and vote on the project by leaving the room, except if the member is providing information at the IRB’s request. If an IRB member realizes at a meeting that he or she may have a conflicting interest in a given project, then that should be disclosed to the IRB Chair immediately, orally and in writing on the IRB Member [Conflict of Interest Declaration](#).

Consultant’s Disclosure of a Conflicting Interest

The definition of conflicting interest as defined in the [Guidelines for IRB Members on Conflicting Interest](#) [GUI-I5] extends to any consultant who may be asked to review a protocol. The IRB Manager who contacts a consultant to enquire about review of a project is responsible for asking if the consultant has a conflicting interest in the project. If such an interest exists, then the protocol will not be assigned to the consultant. If no COI is declared, the consultant is asked to complete a [Consultant Conflict of Interest Declaration](#) for inclusion with the minutes of the meeting.

If a consultant with a conflicting interest is the only appropriate resource for the IRB (e.g., is the only scientist with sufficient technical understanding of the project), and if that consultant has been asked to provide information to the IRB, then the conflict of interest must be disclosed to the IRB members reviewing the protocol or present in the convened meeting where the information is presented. Such a consultant is excluded from discussion except to provide information requested by the IRB and must leave the meeting room during discussion and voting.

IRB Staff and Conflicting Interest

IRB staff must not participate in the review of research protocols and must not make exempt determinations for research protocols in which they have a conflict of interest. IRB staff who realize they have a conflicting interest when they are first assigned a protocol or report for review must notify their supervisor immediately so that the protocol can be reassigned.

The Stanford Staff Policy on Conflict of Commitment and Interest ([Administrative Guide Memo 1.5.2](#)) is distributed annually to IRB Staff who are involved in protocol review.

6.6.1 Separating Competing Business Interests from Ethics Review Functions

Stanford has and follows written policies and procedures to separate competing business interests from ethics review functions. (AAHRPP Element II.1.C)

Stanford recognizes that officials who administer research programs, and individuals who are responsible for development activities (including raising funds), may represent competing business interests, or be in a position to influence programmatic and budgetary decisions and exert undue influence on IRBs or individual IRB members. To avoid such influence on IRB determinations, the Vice Provost and Dean of Research, School Deans, and other Stanford University officers will not serve as voting members of the IRBs, unless there are compelling reasons to do so. Such reasons must be justified in writing, approved by the President of Stanford University, and include specific measures to manage any conflict of interest or the possibility of undue influence.

Research Policy Handbook RPH 4.7 [Institutional Conflict of Interest in Research Involving Human Subjects](#) describes principles and procedures designed to ensure that research involving human subjects at Stanford University is conducted without untoward influence resulting from either the University's financial investments or holdings or the personal financial interests or holdings of key institutional leaders (which can include the President, the Provost, the Vice Provost and Dean of Research, School Deans, Senior Associate Deans, Department Chairs, Division Chiefs, and Institute and Center Directors.)

As stated in RPH 4.7 [Institutional Conflict of Interest in Research Involving Human Subjects](#), Department chairs are required to review and sign off on all research proposals being submitted by faculty in their departments, divisions or institutes, including those involving human subjects research. This review occurs when the proposal is submitted for funding to an extramural sponsor (as part of the electronic submission of the Proposal Development & Routing Form, PDRF) or in meeting their obligation to provide scientific evaluation when internal funds are used to support a human subjects research project. In carrying out these duties, the chair must identify any personal financial conflict of interest, regardless of value, that he or she has in the research sponsor or in an entity that owns or controls the investigational product that is the subject of the research.

Thus, the institutional leaders, as described above, do not:

- Serve as members on the IRB.

- Carry out day-to-day operations of the review process except as noted above.

As stated in the charges to the IRBs, “...neither the Vice Provost and Dean of Research, nor the Provost, nor any other Stanford official or committee may approve a protocol that has not been approved by the decision of one of the Panels, nor apply undue pressure on the Panel to reverse a decision (as further provided in [Chapter 3](#) of the HRPP Policy Manual).” See:

- [Charge to the Administrative Panels on Human Subjects in Medical Research](#)
- [Charge to the Administrative Panel on Human Subjects in Non-Medical Research](#)
- [Charge to the Administrative Panel on Human Subjects in Medical Research \(IRB/SCRO\)](#).

6.7 Assessment and Evaluation of the IRB

The IRB has qualified leadership (e.g., chair and vice chair) and qualified members and staff. Membership and composition of the IRB are periodically reviewed and adjusted as appropriate. (AAHRPP Element II.1.B)

The composition and membership of each IRB is evaluated annually by the RCO Director and the Vice Provost and Dean of Research and is adjusted as needed to ensure appropriate knowledge of applicable regulatory and legal requirements; knowledge of professional standards and practices; knowledge of the local research context and research sites and their capabilities; knowledge of community standards and attitudes; scientific, scholarly, clinical, and professional expertise; racial, ethnic, and cultural diversity; and representation of participants’ perspectives. Due to the increased complexity of human research protocols submitted, this often results in adding members. The composition of each IRB may change annually as needed.

Education, training and periodic evaluation of IRB members, IRB Chairs, and IRB staff is discussed in [Chapter 4](#).

6.8 IRB Roster and Quorum Requirements

The IRB membership permits appropriate representation at the meeting for the types of research under review, and this is reflected on the IRB roster. The IRB has one or more unaffiliated members; one or more members who represent the general perspective of participants; one or more members who do not have scientific expertise; one or more members who have scientific or scholarly expertise; and, when the IRB regularly reviews research that involves vulnerable participants, one or more members who are knowledgeable about or experienced in working with such participants. (AAHRPP Element II.1.A)

The IRB has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan. (AAHRPP Element II.1.E)

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IRB Rosters are constituted to meet the requirements of 45 CFR 46.107 and 108; 21 CFR 56.107 and 108. In addition, membership of those IRBs which review VA research comply with the requirements of 38 CFR 16.103(b), 108(b) and [VHA Directive 1200.05](#).

An IRB Member database is maintained by the RCO and used as the data source for all IRB membership roster needs. The IRB Member database includes all information required under FDA and/or DHHS regulations and OHRP guidance (45 CFR 46.107 and 108; 21 CFR 56.107 and 108) including:

- Names of members
- Names of alternate members (and regular members for whom they substitute)
- Gender
- Earned degrees
- Scientific status
- Representative capacity
- Affiliation

Representative capacity is presented in enough detail to indicate which appropriate participants can be represented by each member (e.g., children, pregnant women, prisoners). When research protocols include vulnerable participants, a member who is knowledgeable about that population, or who has experience working with similar participants, should be assigned to the protocol review.

Scientific status, (including the designation of “nonscientist” – see [Chapter 6.3](#)), is determined during recruitment and annually upon evaluation of IRB members. Scientific status and area of scientific expertise (e.g., pediatrician, radiologist, psychologist, anthropologist, pharmacist) are presented in sufficient detail to allow appropriate protocol assignment and in-depth protocol review.

Affiliation is determined during recruitment and annually upon evaluation of IRB members. An IRB member is considered affiliated if he or she, or any member of his or her immediate family, has any employment or other relationship (e.g., current employee, consultant, Board of Directors, current volunteer, trainee, or student) with Stanford University.

The role of unaffiliated members is to represent the general perspective of participants; the [Checklist for Determining if IRB Members are Unaffiliated](#) [CHK-12] is used to determine if members meet the criteria for serving as unaffiliated.

Changes in IRB membership require reporting to OHRP. The HRPP Associate Director (or delegate) submits a revised IRB membership list to OHRP when required. An IRB registration is effective for 3 years; however, when information changes regarding the contact person who provided the IRB registration information or the IRB chairperson, an update/renewal must be submitted to OHRP within 90 days after the changes occur.

VA Requirements: The HRPP must maintain accurate membership rosters for their designated IRB(s) of Record and submit the roster(s) to ORO whenever a new IRB is formed and have available when requested (as required by [VHA Directive 1058.03](#)).

The IRB has positions available for student members, filled when nominated by the ASSU. Student members represent the perspective of participants in much nonmedical research. Senior IRB administrative staff may also be appointed as nonscientist alternate members of the IRBs.

Quorum Requirements and Voting at IRB Meetings

The IRB has and follows written policies and procedures for conducting meetings by the convened IRB. (AAHRPP Element II.2.D)

The IRB Chair is a voting member of the IRB. The Chair determines that quorum is established and maintained, chairs the meeting discussions, and calls for votes as appropriate.

Maintenance of quorum and voting at convened meetings is based on the following standards:

1. A majority of the (voting) members of the IRB (or their designated alternates), including at least one member whose primary concerns are in nonscientific areas, must be present to conduct a convened meeting. In order for research to be approved, it must receive the **approval of a majority** of such members present at the meeting.
2. **Members may be present in person or through audio (telephone) or audio-visual teleconference.** Members present via teleconference shall be noted as such in the meeting minutes, which shall also indicate that the members received all pertinent information prior to the meeting and were able to participate actively and equally in all discussions.

The standard for members participating by audio or video conferencing is the same for those attending in person, giving all members the opportunity to participate fully in IRB deliberations.

3. IRB minutes shall include documentation of quorum and votes for each IRB action and determination by recording votes as follows:
 - Total number voting
 - Number for
 - Number opposed
 - Number abstaining
 - Names of those abstaining
 - Names of those recusing.

Votes are indicated by voice vote or show of hands.

4. **Members leaving the meeting room** due to a conflicting interest, or for any other reason, will not be recorded as part of the quorum for a particular protocol.

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5. An **individual who is not listed on the official IRB membership roster** may not vote with the IRB.
6. A **non-voting ex-officio member** of, or representative to, a Stanford IRB may not vote with the IRB.
7. **Ad hoc consultants** may not vote with the IRB.
8. A **nonscientist** must always be present for any vote to be taken.
9. Regular attendance of **unaffiliated** members is strongly encouraged. Individual members of the IRB may satisfy more than one required type of member (i.e., a nonscientific member may also be an unaffiliated member).
10. **When a member and their alternate both attend a meeting**, either person (but not both) may vote on each protocol.

Generally, if one of these individuals was the primary reviewer of a given protocol for that review cycle, that person votes on the protocol at the convened meeting.
11. **Voting by proxy** is not permitted.
12. **If the quorum fails during a meeting**, such as due to lack of a majority of IRB members being present or an absence of a nonscientist member, the IRB cannot take any further actions or vote until the quorum is restored.
13. The **IRB Manager is responsible for monitoring** the members present at a convened IRB meeting to ensure that at the beginning of the meeting and for each subsequent vote the meeting is appropriately convened.
14. When the IRB reviews research that **involves participants vulnerable to coercion or undue influence**, at least one member must be present who is knowledgeable about or experienced in working with these participants.
15. When the IRB reviews **research that involves prisoners**, a majority must have no association with the prison involved, apart from their membership on the IRB.
16. When the IRB reviews **research that involves prisoners**, at least one voting member at the IRB meeting must be a prisoner or a prisoner representative with appropriate background and experience to serve in that capacity.
17. If there is no member with appropriate expertise on the panel, or if a consultant with appropriate expertise has not reviewed the protocol in depth, the IRB will defer the discussion of the protocol to another meeting.

See [Chapter 8.3](#) for information about convened meeting minutes.

6.9 Meeting Times and Materials

The IRB has and follows written policies and procedures for conducting meetings by the convened IRB. (AAHRPP Element II.2.D)

Medical IRB Panels 1, 3, 4, 5, and 7 meet each month according to a regular [schedule](#). Generally, protocol applications for convened review that are received by the first of the month (submission date) are reviewed no later than the following month.

Nonmedical panel, IRB 2, meets as needed to review regular protocols. Generally regular and expedited review protocol applications received during that month are reviewed by the end of the month.

IRB Panels 6 and 8 utilize only expedited review procedures. Protocol applications are received on a rolling basis and based on volume are assigned to target dates for review, either the 15th or the last day of each month.

Individual meetings may be rescheduled, or additional meetings may be held, as needed by agreement of the IRB Chair and the RCO Director.

The deadline for receipt of research proposals to the IRBs is the first working day of the month preceding an IRB meeting. For example, the deadline for the March meeting is February first. However, if there is room on the agenda of an upcoming IRB meeting, and sufficient time (generally, a minimum of 72 hours) for review of all relevant materials by the IRB members, research protocols can be placed on an earlier agenda, as deemed necessary by the IRB Chair or IRB staff.

Protocol materials are available online, via the web-based “eProtocol” system: all IRB Members in attendance at a convened meeting are provided individual laptop computers to access eProtocol, and pertinent material is also projected. A hardcopy set of the most commonly referenced guidance are available for IRB members, in addition to being available online through the laptop provided. For videoconference meetings, all materials are available online.

Review and Preparation Time

Protocol Materials

The RCO staff assigns protocols in sufficient time for them to be reviewed before the meeting, generally two to four weeks, but usually not later than 72 hours before an upcoming meeting. Assignment is done via the eProtocol system; this immediately makes available all necessary protocol materials to the primary reviewers. All other IRB members are granted view access to the presented protocol materials, generally 5-7 days prior to the convened meeting.

Materials necessary for review may be presented to IRB members less than 72 hours prior to a meeting only were determined necessary by the IRB Chair or HRPP Associate Director.

For protocol materials provided to members, see [Chapter 7.5](#) and [7.7](#).

Meeting Documents

Approximately five days prior to the IRB convened meeting, all members receive:

- Minutes from the previously convened meeting
- Agenda List and Approval List, containing:
 - Protocols which will be presented at the upcoming meeting,
 - Protocols not presented at the meeting (new, minor modifications, or continuing reviews) which have been reviewed and approved by the expedited process, or reviewed by exempt review, since the prior convened IRB meeting, and
 - Other items (such as Reports which have not required presentation at the convened meeting).

The Agenda, Agenda List containing the presented protocols are issued to members at the beginning of the convened meeting. The agenda includes the following:

- A statement on confidentiality of meetings,
- A conflict of interest statement,
- The Criteria for IRB Approval of Research, and
- Education and information items.

A list of protocols not presented at the meeting (i.e., reviewed by the expedited process) and the minutes from the previous meeting are also available at the meeting.

Ch. 7: Systematic Review

The IRB has and follows written policies and procedures to conduct reviews by the convened IRB: (AAHRPP Element II.2.E)

Element II.2.E.1. – Initial review

Element II.2.E.2. – Continuing review

Element II.2.E.3. – Review of proposed modifications to previously approved research

The IRB has and follows written policies and procedures to conduct reviews by an expedited procedure, if such procedure is used. (AAHRPP Element II.2.F)

Element II.2.F.1. – Initial review

Element II.2.F.2. – Continuing review

Element II.2.F.3. – Review of proposed modifications to previously approved research

7.1 Protocol Review

All Stanford new human research (as defined in [Chapter 1.3](#)) and modifications to approved research (except when the modification is necessary to eliminate apparent immediate hazards to participants) must be **prospectively** reviewed by the IRB. In addition, no previously approved human subject research may be continued beyond the expiration date without prospective approval (continuing review).

7.2 IRB Protocol Applications (eProtocol System)

Most submissions to the IRB are via an online web-based system called “eProtocol”. Forms available for online submission include:

- Protocol applications for:
 - Human Subject Research (HSR) Determinations
 - New protocols
 - Modifications
 - Continuing Review
 - Single IRB (sIRB)
 - Single Patient IND/IDE
 - Humanitarian Use Device (HUD)
- Reports (of unanticipated problems, serious or continuing noncompliance, suspensions, terminations, and events and other information requiring prompt reporting to the IRB)
- Final Reports

Protocol applications include sections that must be completed by the investigators, as applicable. The eProtocol questions include information that will allow the IRB to assess whether the criteria for IRB approval have been met (45 CFR 46.111 and 21 CFR 56.111). A

“check for completeness” feature requires that each question applicable to the study is answered before submission to the IRB is permitted.

Investigators must select a protocol **form type** (medical or nonmedical) and protocol **review type** (HSR Determination, chart review, exempt, expedited, regular, sIRB, single patient IND/IDE, Humanitarian Use Device [HUD]). eProtocol application questions vary depending on the review type and protocol form type selected.

Protocol Application Form

Medical Protocols: Protocols conducted by personnel within, or conducted through, the School of Medicine (SOM) or the hospitals, the Veterans Affairs Palo Alto Health Care System (VAPAHCS), the Palo Alto Veterans Institute for Research (PAVIR), or otherwise involving any medical procedure or use of personally identifiable health information are submitted on the medical Protocol Application.

Nonmedical Protocols: Protocols for research not being conducted by personnel within, or conducted through, the School of Medicine or the hospitals (e.g., protocols from the Schools of Education, Engineering, Earth Sciences, Humanities and Sciences, Law and Business) are submitted on the nonmedical Protocol Application.

Protocol Form Types

Before starting an eProtocol application, investigators must identify the appropriate Review Type. eProtocol then generates the appropriate form type for that [review](#).

Other Research or Special Situations

VA Research: For proposed research, IRB Managers, during pre-review, must complete and attach CHK-07 [Research Involving VA Studies](#) to the IRB Application. Refer to AID-27 [Reviewing Veterans Affairs \(VA\) Research](#) for additional VA guidance.

Additional Requirements – Other Federal Agencies: Depending on the source of support for research, regulations from other agencies such as DOD, etc. might apply. See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for these special considerations and for links to checklists to help ensure that all special considerations are met. IRB Managers, during pre-review, identify these requirements and confirm that they are documented.

Protocols Using Biological Agents or Recombinant DNA Vectors: Investigators are required to submit a Protocol Application to the IRB which includes human participants and the use of biological agents or recombinant DNA and a separate eProtocol application to the Biosafety Panel to address the Biosafety requirements. The Biosafety Panel application is linked within the IRB application for review by both Panels.

Emergency Use of a Test Article: [Chapter 5.8](#) describes the requirements for the emergency use of an investigational drug, device, or biologic under FDA regulations at 21 CFR 56.104(c), and materials which must be submitted to the IRB.

The submitted material is received by the IRB Office and the materials are provided to an IRB Chair or their designee. If the IRB staff person or the reviewer has comments they are sent to the investigator for response. Responses are reviewed and additional comments sent if needed. The reviewer documents their findings on the [Exemption from IRB Review: Emergency Use of a Test Article](#).

7.3 Submission, Preliminary Review and Assignment to IRBs – New Protocols, Modifications, Continuing Review, Reports, Final Reports

Submission and Preliminary Review - New Protocols

Upon receipt of a new Protocol Application, the IRB intake staff reviews the application for completeness, including ensuring all required supplemental documents and information are provided. The IRB intake staff also performs a preliminary review to confirm the PD’s selection of the form type and protocol review type.

Protocols submitted for a review that are determined not appropriate are converted to the appropriate review type by RCO staff. If the change in review type requires additional information from the PD, the protocol is returned to the PD. If the conversion does not require additional information, the protocol is assigned to an IRB. If the nonmedical IRB manager receives an incorrect form type, i.e., a protocol that should be reviewed by a medical IRB, the protocol is returned so it can be submitted on a medical IRB eProtocol application.

Assignment to IRBs - New Protocols

Once a new Protocol Application is deemed complete, the protocol is assigned to an IRB for review. To avoid any potential conflicting interest, new medical protocols are generally not assigned to an IRB where a member of that IRB is also an investigator on the research project. After taking into consideration any conflicting interest issues, assignment of medical protocols to IRBs is based on the protocol review type, the order (by date) the protocol was submitted to the IRB, and for protocols subject to regular review the order of the monthly IRB meetings:

Medical protocols subject to expedited and exempt review are generally assigned to IRBs 6 and 8. IRB 6 reviews only medical protocols; IRB 8 reviews both medical and some existing nonmedical protocols.

Medical protocols subject to regular review are assigned to IRBs 1, 3, 4, 5 and 7 with assignment to the next IRB starting after the preceding IRB has reached its protocol load for that meeting.

Nonmedical protocols subject to regular, expedited, or exempt review are assigned to IRB.

HSR Determination applications are assigned to IRB 6, 8, and 98.

sIRB applications are assigned to IRB 99.

Special Assignment Considerations:

Protocols involving biological agents or recombinant DNA vectors (gene transfer) are assigned to IRB 1. Protocols involving prisoners are assigned to IRBs with a prisoner representative.

Generally, protocols involving both human subject and stem cell research are assigned to IRB 3.

All subsequent events submitted on approved protocols are received directly by the IRB that last reviewed and approved the protocol. When necessary, protocols may be moved to another panel with all related reviews and event history included.

7.4 Assignment of protocols to IRB members

The IRB has and follows written policies and procedures requiring research protocols or plans to be reviewed by individuals with appropriate scientific or scholarly expertise and other expertise or knowledge as required to review the research protocol or plan. (AAHRPP Element II.1.E)

Reviewer assignments are made with the objective of matching reviewer expertise and experience with protocol subject matter. See [Chapter 6](#). “Nonscientific” members assigned to review protocols are valued for the community perspective they bring to the process of ensuring the protection of research participants. For approved protocols an attempt is made to assign subsequent protocol events to a member who has previously reviewed the study.

Protocols Subject to Regular Review – New, Modifications, Continuing Review and Reports

New Protocols: The medical and nonmedical IRBs utilize a primary reviewer system for protocols subject to regular review. New regular protocols mostly are assigned by the IRB manager to a minimum of two primary reviewers, with one of the primary reviewers assigned to present the protocol at the convened meeting. The IRB manager assigns other expert reviewers to protocols when applicable (e.g., Radiation Safety when a project involves radiation producing machines). When a study may be moved to expedited 9 or an MPP/shell study, one primary reviewer is assigned.

If there is not at least one person on the IRB with the appropriate scientific or scholarly expertise, or other expertise or knowledge, to conduct an in-depth review of the protocol, the IRB defers to another meeting, to another IRB, or obtains consultation.

The IRB manager, primary IRB reviewer, or IRB Chair can determine whether a consultant is needed. The process by which this is done is described in [Chapter 6.5](#).

Modifications: The following modifications are subject to regular review and are assigned by the IRB manager to one reviewer who reviews and presents the protocol at the convened meeting:

Major (or “Substantive”) Modifications: A major (substantive) modification is one in which there is an increase in the level of risks to participants or a greater than minor modification in any of the following:

- The consent form
- Research design or methodology
- The subject population enrolled in the research
- The qualifications of the research team
- The facilities available to support safe conduct of the research
- Any other factor which would warrant review of the proposed changes by the convened IRB.

Major modifications that are submitted at least 72 hours prior to the convened meeting of the assigned panel are generally reviewed and presented at that convened meeting. If submitted later, assignment is to the following convened meeting. Once approved, documentation of the change is immediately available in eProtocol.

Continuing Review: For all protocols initially subject to regular review, the continuing review application undergoes regular review, unless it meets the criteria for expedited review (see below). Those which will undergo regular review are assigned to one reviewer who reviews and presents the protocol at the convened meeting.

Reports (unanticipated problems, serious or continuing noncompliance, suspensions, terminations, and events and information requiring prompt reporting): See [Chapter 3.10](#).

IRB Notification to Organizational Offices and Officials

The IRBs notify organizational offices and officials, in writing, of their findings and action and IRB minutes are made available to the Vice Provost and Dean of Research. The RCO Director reviews issues addressed in the minutes with the Vice Provost and Dean of Research when needed or during regularly scheduled meetings.

See OHRP guidance [Categories of Research That May Be Reviewed by the Institutional Review Board \(IRB\) through an Expedited Review Procedure](#).

The IRB has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance. (AAHRPP Element II.4.A)

Additional Requirements

Depending on the type of research project, or the source of support/funding for the study or institution at which the study will be conducted (e.g., Department of Defense), other additional requirements might apply.

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] and [VHA Directive 1200.05](#).

Protocols Subject to Expedited Review – New, Modifications, Continuing Review, Reports, and Final Reports

Expedited reviews are assigned by the IRB manager either to the Chair of the IRB or to an IRB member designated by the Chair as qualified to conduct expedited review. See [Chapter 6](#) for reviewer qualifications, and [Chapter 4](#) regarding evaluation of IRB members which is completed annually.

New Protocols: Protocols subject to expedited review follow a single reviewer process and are assigned by the IRB manager either to the Chair of the IRB or to a qualified IRB member. The expedited member shall provide rationale for their determination for when research appearing on the expedited review list described in 45 CFR 46.110(a) is more than minimal risk.

Modifications (Minor): A minor modification eligible for expedited review is one in which all of the following are true in the judgment of the IRB reviewer:

1. Any increment in risk is less than minimal risk.
2. All additional activities or procedures would have been eligible for expedited review had they been part of the initial protocol review.
3. Either the research is minimal risk, or the proposed changes do not alter the study design.

Minor modifications can be submitted at any time during the month and are reviewed and approved on a first-come, first-served basis. Documentation is available in eProtocol upon approval. If the modification changes the review type appropriate for the study, the IRB staff will convert the application form to the appropriate review type. The IRB reviewer makes the final determination of whether changes to the protocol are “major” or “minor.”

Continuing Review (Protocols subject to regular review initially): For a protocol initially subject to regular review, but not eligible for an extended approval period under the Extended Approval Process, the continuing review application undergoes expedited review:

If (expedited category 8):

- (i) the research is permanently closed to enrollment of new subjects; (ii) all subjects have completed all research-related interventions; and (iii) the research remains active only for long term follow-up of subjects; or
- No subjects have been enrolled and no additional risks have been identified; or
- The remaining research activities are limited to data analysis,

or (expedited category 9):

- For continuing review of research, not conducted under an investigational new drug application or investigational device exemption where categories two (2) through eight (8) do not apply but the IRB has determined and documented at a convened meeting that the research involves no greater than minimal risk and no additional risks have been identified.

Protocols subject to expedited continuing review are assigned to one reviewer and are not presented at a convened meeting.

Continuing Review (Protocols subject to expedited review initially): For a protocol initially subject to expedited review, but ineligible for an extended approval period under the Extended Approval Process, the continuing review application undergoes expedited review when:

- It does not include any modifications, or
- If modifications are included, the proposed modifications would have been eligible for expedited review had they been part of the initial protocol.

Protocols subject to expedited continuing review are assigned to one reviewer and are not presented at a convened meeting. The IRB shall provide rationale for conducting continuing review of research that otherwise would not require continuing review as described in 45 CFR 46.109(f)(1).

Continuing Review (Protocols subject to Extended Approval Process initially): For a protocol initially approved with an extended approval period under the Extended Approval Process, the continuing review application must be submitted only when the study is no longer eligible for extended approval (see Chapter 7.8).

Reports (unanticipated problems and events and information requiring prompt reporting): See [Chapter 3.10](#).

Final Reports: Final Reports are acknowledged and serve as documentation of study closure.

7.5 Protocol Review Material and Information

Upon protocol assignment, the reviewers and IRB staff have full access to all protocol information and materials submitted. Review materials always include the Protocol Application. Depending on the protocol event under review, the Protocol Application will be supplemented with a Modification, Continuing Review (including a status report on the progress of the research), Report or Final Report setting forth the dispositive information supporting the event.

In addition, reviewers have access to all documents submitted in support of the Protocol Application which may include as applicable:

- Informed consent and assent documents
- Recruitment materials, including advertisements
- Questionnaires and surveys
- Information sheets/brochures or other study related materials that participants receive

- Supporting protocol (e.g., industry sponsor or DHHS-approved protocol)
- DHHS-approved informed consent document
- Investigator’s brochure (drugs)
- Device manual or report of prior investigations (devices)
- All relevant reports, including multi-center trial reports (at continuing review)

Additional information may be requested to complete the review of a protocol.

7.6 Protocol Review - Pre-Review Parallel Process

General Process for All Protocol Events

The medical and nonmedical IRBs utilize a parallel process of pre-review, which involves an interactive review process between primary reviewer(s), IRB staff, and investigators. For protocols assigned to a convened meeting, this system allows all presented protocols to be reviewed by the primary reviewer(s), so that recommended changes to the protocols have been made and questions answered when the protocol is presented for discussion and review by the convened members.

Generally, within 24 hours after the convened meeting, the IRB notifies investigators in the eProtocol system of its decision to approve proposed human research activities.

Comment and Response Cycle(s)

During the parallel review of a protocol, the IRB staff and primary reviewer(s) enter any comments or questions or recommended changes to the protocol or associated documents (e.g., consent forms, advertisements) stemming from their review into the eProtocol Comments/Responses page. After reviewing and editing all comments received for consistency and duplication, the IRB staff sends the comments to the investigators. Investigators are notified via an auto-generated email that comments have been sent on the protocol. All comments are sent without referencing the author of the comment, thus preserving their anonymity. Comments are sent out with a request for response within three business days.

Upon return receipt of the investigators’ responses to the comments and recommended changes to the protocol and associated documents, the IRB staff review the responses and changes for completion then forward responses to the primary reviewers who review the comments and changes in turn. If additional questions remain or changes need to be made, another round of comments is generated and sent to the investigators for responses. This process is repeated as often as necessary, until all reviewer questions have been answered and requested changes to the protocol and documents have been made.

Protocols may be moved for review to a subsequent meeting pending receipt of additional substantive information or if the comments and response cycles are not completed prior to the convened meeting. The IRB manager notifies the PD that the protocol was moved and why it was moved.

Approval Criteria

All proposed research must meet Stanford HRPP ethical standards governing the conduct of research (e.g., acceptable risk-benefit relationship, equitable selection, informed consent, protections of privacy, maintenance of confidentiality, and protections for vulnerable populations). The reviewers consider the approval criteria set forth in 45 CFR 46 and 21 CFR 50 in reviewing and approving a new protocol, continuing review, or review of a modification when the modification affects a criterion for approval. The IRB confirms that proposed Protocol Application, informed consent documents, and other supporting documents are accurate and complete.

The reviewers consider the regulations in reviewing and approving a protocol. They are aided in their consideration by regulatory guidance provided in the form of:

- [Criteria for IRB Approval of Research](#)
- [General Requirements for Informed Consent](#)

Review of Exempt Research

See [Chapter 3.5](#).

Continuing Review

Unless the study is approved with an extended approval period under the Extended Approval Process, submission of a protocol for continuing review is required on all non-exempt approved protocols where research activities are ongoing, including but not limited to continuing recruitment and enrollment of participants; research tests, procedures, and other interactions and interventions; review of identifiable information; data analysis; and follow-up of previously enrolled participants.

The eProtocol system automatically identifies all protocols that will expire prior to the next IRB panel meeting date. Expedited panels do not meet but do have meeting dates in order to follow continuing review and expiration processes. Notices are sent two months prior to the expiration date, and again a month before expiration if a continuing review (renewal) form has not yet been received. The Protocol Director is ultimately responsible for maintaining approval. Expiration Notices are sent when the protocol expires.

Continuing review may stop only when:

- Stanford's Extended Approval Process (See [Chapter 7.8](#)) applies to the study, or
- All of the following are true:
 - The research is permanently closed to the enrollment of new participants, and
 - All participants have completed all research-related interventions, and
 - Collection and analysis of private identifiable information has been completed.

The continuing review of protocols that also include proposed modifications to a previously approved project, including supporting documents (e.g., consent forms, advertisements, sponsor protocol) or the addition of new documents, must be accompanied by the new documents or the proposed revised versions of the previously approved or submitted documents. The IRB considers all information in determining whether changes are needed in the protocol or consent form.

The IRB determines whether the protocol needs verification from sources other than the researchers that no material changes had occurred since previous IRB review based on random reviews conducted by the Continuous Quality Improvement team or where concerns have been raised by reports of non-compliance or continuing review submissions.

Modifications

No modifications may be initiated without prior approval of the IRB, except where necessary to eliminate apparent immediate hazards to participants. Investigators are required to complete a Modification application setting forth a summary of the proposed modification and indicate the change in the risks to participants associated with the modification (e.g., increase, decrease, no change). Modifications involving changes to previously approved or submitted documents, (e.g., consent forms, advertisements, sponsor protocol) or the addition of new documents, must be accompanied by the new documents and/or the proposed revised versions of the previously approved or submitted documents.

In the rare situation where a modification is made without prior IRB approval because it is necessary to eliminate apparent immediate hazards to subjects, the investigator must report this change to the IRB, (see guidance [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13]). The IRB will determine whether the change was consistent with ensuring the participants' continued welfare. See [Chapter 3.10](#).

If significant new findings or information are submitted as part of a modification or continuing review, the IRB may require the reporting of this information to participants if the information could reasonably affect participants' willingness to continue participation.

Final Reports

Upon completion of a research project investigators may be required to submit a Final Report notifying the IRB of the completion of the project.

Final Reports are **required** for:

- Research that was subject to regular review,

Final Reports are **not required** for:

- Research subject to expedited* or exempt review

Additional Requirements: Federally-Supported Research Involving Surveys

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for other requirements, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy).

Protocols Using Biological Agents or Recombinant DNA Vectors

The review processes described above for protocols subject to regular review are used for protocols using biological agents or recombinant DNA vectors, except for the following:

The protocols must also be approved by the Biosafety Panel (IBC). Generally, the Biosafety Panel reviews protocols first, and then they are reviewed by the IRB. IRB approval cannot be granted until approval by the Biosafety Panel has been granted. (To prevent a protocol from expiring, the IRB may approve the continuation of the protocol contingent on Biosafety Panel approval. No new research participants may be enrolled until both Biosafety and IRB approval is granted.)

Protocols Using Radioactive Drugs

Protocols using radioactive drugs such as tracer or imaging compounds are reviewed by the local FDA-approved Radioactive Drug Research Committee (RDRC). The determination of the RDRC is transmitted to the IRB through Radiation Safety reviewers. The RDRC can only approve research with radioactive drugs in accordance with the regulations ([21 CFR 361](#)). The RDRC may recommend that an investigator obtain an IND from the FDA if the RDRC determines that it is outside its purview.

Range of Action for Decisions on Protocols Subject to Expedited Review

The reviewer(s) of protocols subject to expedited review act on behalf of the IRB and have the authority to approve, require modifications (to secure approval) or request full committee review of the protocols. The reviewers consider the approval criteria set forth in 45 CFR 46.111 and 21 CFR 56.111 in reviewing a protocol. The IRB confirms that proposed Protocol Application Form, informed consent documents and other supporting documents are accurate and complete. The IRB notifies the investigator via the eProtocol system about any IRB actions and determinations (e.g., Approval, Contingent Approval, Moved to Regular Review). Approval Lists of all non-presented events are sent monthly to all respective panel members. The possible decisions are:

1. **Approved:** After the reviewer(s) approve, the protocol is entered on a list that is circulated to all IRB members before the next meeting for the IRB and again at the convened meeting. (Note IRBs 6 and 8 only review protocols subject to expedited and exempt review and do not have regularly scheduled meetings. The list of protocols is circulated to all members of the IRB via email.)
2. **Modifications are required to secure approval:** The IRB Manager informs the PD in writing via eProtocol of any reviewer modifications, comments, questions, or concerns

about the protocol and requests a reply within a specified time via the eProtocol auto generated email; the research may not proceed until the responses have been reviewed and the protocol has been approved.

3. **Moved to Regular Review:** The protocol raises questions that warrant regular review, the study is greater than minimal risk or does not fit into an expedited category, or PD does not agree to the modifications required for approval, the reviewer will request that the protocol be presented for regular review at the next convened IRB meeting.
4. **Decision to not approve:** A single IRB reviewer cannot reject or not approve a protocol; thus, a reviewer using the expedited procedure may not disapprove research. A protocol can only be not approved (rejected) by a vote at a convened IRB meeting.

Protocols subject to regular review are presented and voted on at a convened IRB meeting with a quorum of reviewers present.

7.7 Protocols Presented at a Convened Meeting

The IRB has and follows written policies and procedures for conducting meetings by the convened IRB. (AAHRPP Element II.2.D)

Quorum

A quorum for the IRB is at least half of the voting membership plus one, including a member whose primary concern is in a nonscientific area. When the agenda for a specific meeting includes a protocol enrolling prisoners the prisoner representative must attend [and vote] on the prisoner protocol. Expert reviewers are not required to attend the convened meeting, although they are sometimes invited to do so, and they do not vote.

Materials Available at Convened Meetings

Prior to the convened meeting, all scheduled voting IRB members, including non-primary reviewers, are notified of electronic access to all protocols to be presented. This electronic access enables reviewers to see the entire protocol submission, including the application and any reports (e.g., modification, continuing review, reportable event), all comments and responses, assent and consent form(s) and all other documents associated with the protocol (e.g., telephone script, questionnaires or surveys, advertisements). Reviewers are expected to review the information sufficiently to provide comments (if any) before the meeting and during the meeting. All materials submitted supporting a protocol are also available to voting members during the meeting.

In addition, all members are provided the Meeting Agenda, Agenda List of presented protocols, and list of protocols not presented at the meeting. Color-coded laminated guidance documents (e.g. [Additional Protections for the Inclusion of Children in Research \(OHRP\)](#) for 45 CFR 46.404, 405, 406, 407 and 408; [Regulations for Waiver or Alteration of Consent Requirements](#) for 45

CFR 46.116, 117) are made available for IRB members. See Human Subjects Research website [Guidances](#) page.

Meeting Deliberations

The primary reviewers are considered the lead reviewers on the IRB for protocols assigned to them. They are responsible for:

- Being thoroughly versed in all details of the research,
- Conducting an in-depth review of the research using the IRB reviewer forms and tools as guidance.

The primary reviewer designated as the presenter presents the protocol for discussion. All IRB members are afforded full opportunity to discuss each research protocol during the convened IRB meeting. The reviewers consider the approval criteria set forth in 45 CFR 46 and 21 CFR 50 in reviewing a protocol. The IRB confirms the proposed protocol application, informed consent documents, and recruitment documents are accurate and complete. Controverted issues are discussed at the convened IRB meeting.

Procedure for Special Findings When Approving a Protocol

The reviewers and voting members consider the following information and regulations to make any special findings in reviewing and approving a protocol. They are aided in their consideration by regulatory guidance provided in the form of color-coded laminated guidance documents, including:

Frequently referenced guidances (laminates)	Laminate color
Criteria for IRB Approval of Research	
General Requirements for Informed Consent	
Additional Protections for the Inclusion of Children in Research (OHRP) When the protocol involves children as participants, the IRB considers all of the regulations of 45 CFR §46.404, 45 CFR §46.405, 45 CFR §46.406, 45 CFR §46.407, 45 CFR §46.408 to make the appropriate finding(s) under which the children may be included. Wards: When the protocol involves children who are wards of the state the IRB considers all of the regulations of 45 CFR §46.406, 45 CFR §46.407 and 45 CFR §46.409(a) to make the appropriate finding(s).	

Frequently referenced guidances (laminates)	Laminate color
<p>Additional Protections for the Inclusion of Children in Clinical Investigations (FDA)</p> <p>When the protocol involves children as participants, the IRB considers all of the regulations of FDA 21 CFR §50.51, FDA 21 CFR §50.52, FDA 21 CFR §50.53, FDA 21 CFR §50.54, and FDA 21 CFR §50.55 to make the appropriate finding(s) under which the children may be included. Wards: When the protocol involves children who are wards of the state the IRB considers all of the regulations of FDA 21 CFR §50.53, FDA 21 CFR §50.54 and FDA 21 CFR §50.56(a) to make the appropriate finding(s).</p>	
<p>Guidelines for IRB Members on Conflicting Interests</p>	
<p>Regulations for Waiver or Alteration of Consent Requirements</p> <p>When the investigator requests waiver or alteration of informed consent in the protocol application, the rationale for the waiver or alteration is considered by the IRB as it makes any finding of waiver or alteration of informed consent as required by 45 CFR §46.116(e) or 45 CFR §46.116(f).</p>	
<p>Waiver of Documentation (Including Signature) of Consent</p> <p>When the investigator requests waiver of consent documentation in the protocol application, the rationale presented for the waiver is considered by the IRB as it makes any finding of waiver of consent documentation under 45 CFR 46.117(c) and 21 CFR § 56.109(c).</p>	
<p>Significant Risk and Non-significant Risk Medical Devices Studies When the protocol uses an investigational device that the investigator considers to be a non-significant risk, the rationale for non-significant risk is included in the protocol application.</p>	
<p>Research Involving Pregnant Women, Fetuses, and Neonates</p> <p>When a protocol involves pregnant women, human fetuses and neonates, the IRB considers the investigator's response to the items in 45 CFR 46.204, as well as the IRB's review of the items, and makes a finding under 45 CFR §46.204, 45 CFR §46.205, 45 CFR §46.206, and 45 CFR §46.207.</p>	

Frequently referenced guidances (laminates)	Laminate color
OHRP Guidance on the Involvement of Prisoners in Research	
HIPAA and PHI Waiver of HIPAA Authorization: When the investigator requests waiver or alteration of HIPAA authorization for the study, or limited waiver of HIPAA authorization for activities such as recruitment, the IRB considers the rationale presented for the waiver(s) to determine if all of the requirements of 45 CFR 164.512(i)(2)(ii)(A), (B), and (C) are met, and if so, makes the required finding.	
Emergency Use of a Test Article	
Exempt Review Categories	
Expedited Review Categories	
What Qualifies as Human Subject Research	
(1) Clinical Trials Terms (2) Commonly Used Acronyms	
Unanticipated Adverse Device Effect (UADE)	

Additionally, for protocols involving **fetal tissue transplantation**, the IRB considers the investigator's rationale and the risks involved in order to make any finding required by 42 USC §498A (b)(1) and (2).

Range of Actions on Regular Protocols at Convened Meetings

The IRBs must systematically evaluate each protocol to ensure the protection of research participants and reach a decision. The possible decisions are:

- **Approved with no changes:** (or no additional changes). The research may proceed. Approval requires an affirmative vote by a majority of the convened quorum.
- **Contingent:** Approved at a convened IRB meeting contingent on the investigator making minor changes. Such minor changes must be clearly delineated by the IRB at the meetings and approval is contingent on the PD accepting the IRB stipulations or making any verbatim changes to documents requested by the IRB. The research may proceed after the IRB chairperson (or any other individual(s) designated by the IRB) has reviewed

and accepted as satisfactory all changes to the protocol or informed consent documents, or any other responsive materials, required by the IRB from the investigator. This review is carried out via the expedited process).

- **VA research:** If the convened IRB approves the study contingent on specific minor modifications to the protocol or the informed consent form, the IRB Chair, or an experienced IRB voting member designated by the Chair, may use expedited review procedures to verify that the specific minor conditions were met.

If during the meeting the members decide major changes are required, the protocol is tabled.

- **Tabled:** Approvable with greater than minor changes to be reviewed by the convened IRB. The research may proceed only after the IRB has reviewed and approved the required changes to the research at a convened IRB meeting.

A protocol will be tabled until it is approved (or eventually not approved) by the voting members at a convened meeting. If initial reviewers are not available at subsequent meetings where a tabled protocol is reviewed, additional reviewers will be assigned to review and present the protocol.

- **Not approved:** The IRB has determined that the research cannot be conducted at Stanford or under the auspices of Stanford (e.g., the regulatory requirements, Stanford HRPP standards, or other stipulations have not been satisfied). The investigator is provided with a memorandum from the IRB Chair notifying him/her that the protocol was not approved by the IRB, explaining the reason(s) the protocol was not approved, and giving the investigator an opportunity to respond in person or in writing. (Not permissible for protocols undergoing expedited review).

The minutes of the IRB meetings document the deliberations, actions, and votes for each protocol undergoing Regular Review, and include references to the determinations made by the IRB. The eProtocol system notifies the investigator about any IRB actions and determinations (e.g., Approval, Contingent, Tabled, or Not Approved).

Approval Date and Determination of Expiration Date

The approval date for a protocol subject to regular review is the date of the IRB meeting where the protocol was approved. The approval date of a protocol or protocol event (modification or continuing review) subject to expedited review is the date the reviewer recommends the protocol or event for approval. Approval of a modification does not alter the expiration date.

Protocols are approved for a period of no more than one year, except when the Extended Approval Process applies (see [Chapter 7.8](#) below), and unless otherwise stipulated by the reviewers. The expiration date is the last day the protocol is approved (e.g., a protocol approved on January 1, 2030 will expire at midnight on January 1, 2031).

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The IRB can approve a protocol for a shorter period if warranted by the risks presented to participants. The IRB may approve a study for 6 months or may stipulate the approval on further IRB review after a defined number of participants have been enrolled (e.g., review after the first three subjects receive a Phase I drug that has never been tested in humans). If any of the following are true, the IRB may perform review more often than annually: (a) novel high-risk study using new therapeutic modality; (b) phase I studies of a new drug or biologic that has never been tested in humans; (c) studies involving a novel significant risk medical device that has never been tested in humans; (d) a high degree of uncertainty regarding the risks involved; (e) the vulnerability of the subject population; (f) the experience of the investigator; (g) the IRB's previous experience with the investigator and/or sponsor; or (h) other high-risk studies as IRB members deem appropriate (this includes research for which the IRB determines that reports to the IRB of monitoring data should be more frequent than annually).

Extended Approval Process: Continuing review may not be required as long as certain conditions are met. Certain changes in eligible studies may change the IRB review requirement for the extended approval period to an annual review. See [Chapter 7.8](#).

Approval contingent on minor conditions: The protocol initial approval date is recorded as the date the convened IRB approved the study contingent on minor conditions being addressed. However, the "effective" date of initial approval is the date on which the IRB chairperson (or designee) has reviewed and accepted as satisfactory any documents or any other responsive materials required by the IRB; IRB Approval Letters are not 'released' until contingencies have been met. No research study activities involving human subjects may be initiated until the conditions have been satisfied in the manner set forth by the IRB and the approval becomes effective. The **expiration date** is determined in reference to the date the study was approved by the convened IRB contingent on minor conditions being addressed.

Research that continues after the approval period expires is considered research conducted without IRB approval. If investigators fail to apply for continuing review prior to the expiration date, the designated IRB must notify the PDs that research activities -- including but not limited to recruitment, advertisement, enrollment, interventions, interactions, data collection, and data analysis -- are unapproved and must stop, unless the IRB determines that continued involvement is in the best interest of enrolled subjects who are still receiving study-related interventions. (The IRBs do not consider this a suspension or termination under [Chapter 9.3](#), since it is not activity under an "approved" protocol.)

In such a situation, the IRB will notify investigators, through the Notice of Protocol Expiration to submit immediately a list of participants for whom stopping research activities would cause harm. The IRB will determine whether the continued involvement is in the best interests of each individual participant.

VA research: In the case of VA research, the IRB or IRB Chair will consult with the VA Chief of Staff in making this determination. The IRB Chair or designee will provide a written determination to the investigator following consideration of this issue. The IRB also will instruct

the investigator on relevant reporting requirements, including promptly reporting the expiration of approval to the sponsoring agency or private sponsor if any.

7.8 Extended Approval Process

Under 45 CFR 46.109 (f)(1), continuing review of research is not required in the following circumstances:

- Eligible for expedited review (as defined by 45 CFR 46.110)
- Eligible for limited IRB review (as defined by 45 CFR 46.104(d)(2)(iii) and (d)(3)(i)(C))
- Has progressed to the point that it involves data analysis, including analysis of identifiable private information or identifiable biospecimens, or
- Has progressed to the point that it involves accessing follow-up clinical data from procedures that subjects would undergo as part of clinical care.

Stanford University has chosen to limit the scope of its Federalwide Assurance (FWA) to federally funded research by “unchecking the box” on its FWA. This has allowed an appropriate degree of flexibility by also extending the approval period for non-federally funded research approved under the pre-2018 common rule.

Research projects reviewed under the Extended Approval Process will be afforded protections commensurate with risk as determined by the IRB.

All human research projects conducted or supported at Stanford remain subject to Stanford IRB policies and review, whether they are reviewed under this policy or not. When questions of applicability arise, studies will be reviewed on a case-by-case basis.

This process extends IRB approvals through the life of the project with the following exceptions:

- Research involving FDA-regulated components or FDA oversight
- Research funded by the Department of Justice
- Research associated with a SCRO protocol
- Research involving prisoners as participants
- Stanford is the IRB of record
- Studies which have **ever** been federally funded (and approved before 1/21/2019)
- Research involving the VA (and approved before 1/21/2019)

Monitoring

A random sample of studies processed under this policy will be reviewed periodically to confirm that the funding status has not changed to federally sponsored, the level of risk has not increased to more than minimal, and that any changes made to the protocol have been reported to the IRB prior to implementation.

Protocol Status

Every three years, researchers are asked to confirm the study is active.

Reporting Requirements

Research projects outside the scope of the FWA are not subject to federal reporting requirements. For projects conducted under the Extended Approval Process, the Stanford IRB follows internal reporting requirements for serious or continuing non-compliance, suspensions, terminations, or reporting of unanticipated problems involving risks to participants or others, as described in [Chapter 3.9](#) – [3.11](#).

Ch. 8: Documentation of IRB Activities

The IRBs maintain documentation of their activities. IRB records include IRB protocol files, minutes for convened IRB meetings, and other documentation.

8.1 IRB Protocol Files

The IRB maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, Sponsor requirements, and organizational policies and procedures. (AAHRPP Element II.5.A)

The RCO employs an electronic protocol application system, “eProtocol”. Documents are also maintained in the secure server.

Electronic Protocol System (eProtocol)

The eProtocol system maintains electronic records of documents submitted through the system for every protocol event. The eProtocol system contains a search function for locating and retrieving protocols by protocol number, protocol title, name of Protocol Director (PD), names of co-investigators, review type, meeting date, internal funding number, sponsor, IRB number, reviewer, or any combination of the above categories. Electronic copies of materials submitted to the IRB can be accessed through eProtocol or on secure server; thus all documents supporting each protocol event are accessible to reconstruct the entire history of a protocol.

A protocol file contains, as applicable to the research:

1. **Protocol Application(s).** The protocol file includes one or more of the following application types:
 - Protocol Application for medical or nonmedical research (Regular, Expedited, Exempt, single IRB, chart review, single patient IND/IDE, Humanitarian Device, HSR determination) submitted for all new research projects
 - Modification Form, submitted for modifications to approved research
 - Continuing Review Form, submitted for continuing review of research
 - Reports submitted for reportable events and information per guidance [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13]
 - Final Report Form, submitted for closing Regular review protocols.

IRB comments and investigator responses that occurred during IRB review are included with each application. Comments and responses exchanged via fax or email are also included as attachments.

2. ***The IRB-approved informed consent document(s).*** The protocol file includes all approved consent forms, including the currently approved consent form. When a sample DHHS consent form is provided, it is included in the protocol file.
3. ***The IRB-approved Assent form(s).*** If a study involves adult assent or children from whom the investigators will obtain assent, copies of approved assent forms will be included in the protocol file.
4. ***Scientific evaluations of the proposed research.*** Documentation of scientific review is included in the protocol file. See [Chapter 1.7](#) for information on scientific and scholarly review.
5. ***Sponsor Materials.*** For investigational drug studies, the Investigator's Brochure and Sponsor's Protocol, including current amended editions of these documents and all previous versions are included in the protocol file.

For investigational devices, a report of prior investigations and the Sponsor's Protocol are filed.
6. ***Advertisements, phone screening scripts*** and non-medical oral scripts, flyers, website, or other subject recruitment materials.
7. ***Questionnaires, surveys, interview scripts, diaries*** or other documents used in the course of the study.
8. ***Participant informational*** sheets, brochures, and sponsor newsletters.
9. ***Reports submitted for reportable events and information*** per guidance [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13].
10. ***Significant new findings*** developed during the course of the research that may relate to the subject's willingness to continue participation
11. ***Final reports*** submitted for regular protocols.
12. ***Data and Safety Monitoring Board (DSMB) reports, Annual Progress reports.***
13. ***Conflict of Interest (COI) documents*** when COI or ICOI is applicable.
14. ***Correspondence and communication*** between IRB members, IRB staff and investigators.
15. ***Other IRB correspondence*** related to the research.
16. ***Documentation of all actions*** including approvals, disapprovals, waivers or alterations of consents and HIPAA authorizations (as documented in the protocol application forms).
17. ***Documentation of the rationale for conducting continuing review of research that otherwise would not require continuing review*** (as described in 45 CFR 46.109(f)(1))
18. ***Approval letter (or Notice of Exempt Review*** for research subject to exempt review.)

19. ***Documentation of protocol closeout*** if any, including Final Report forms for regular protocols.
20. ***Documentation of the rationale for an expedited reviewer's determination under that research appearing on the expedited review list described in 45 CFR 46.110(a) is more than minimal risk.***
21. ***Expiration notice sent date.***
22. ***IRB approvals from collaborating institutions*** are requested and included in the research file. IRB approval notices are requested from collaborating institutions when Stanford is the coordinating center for a multi-site study, or when data is being received at Stanford. If the study is a multi-site study, with Stanford as one of several participants, no other IRB approval is gathered or included from other participating sites.
23. ***Various IRB checklists*** including Protocol, Reviewer, Informed Consent, Exemption Eligibility, Expedited Eligibility, Expedited Modification Checklist, and Continuing Review checklists.

IRB records are retained under the eProtocol ID number in eProtocol. Some protocol information is also maintained on the secure server. Each protocol file is organized to allow a reconstruction of a complete history of all IRB events related to the review and approval of the protocol. In the event of a local disaster, the eProtocol system is backed up at Stanford's Disaster Recovery site in Livermore. This site houses critical administrative and business systems in support of the University's business continuity efforts. Relocating redundant critical systems affords greater geographic diversity and additional protection in the event of a level three emergency, such as an earthquake on the San Andreas Fault.

Other Documentation Maintained

Information Specific to Certain Types of Research or Special Situations

Emergency Use of a Test Article

Research involving the emergency use of a test article under FDA regulations 21 CFR 56.104(c) is described in [Chapter 5](#). Documentation of the emergency use of a test article is submitted to the IRB within five days of the use of the test article and includes the following documents:

- Emergency Use of a Test Article Notification Form
- Consent form, if applicable

The IRB Chair of a medical IRB or a designated physician IRB member reviews the materials submitted to verify conditions of 21 CFR 56.103(c) have been met, including requirements for informed consent unless the conditions of 21 CFR 50.23(a)-(b) have been met. IRB review is documented by the Exemption from IRB Review for Emergency use of a Test Article.

Human Subject Determination

Human Subject Determination applications, Notices of Determination and any other materials acquired in the process of review of proposed research that has been found to *not* meet the definition of Human Subject Research is kept in a separate file in the Research Compliance Office.

IRB Reliance Agreements

The Research Compliance Office maintains documentation specifying the responsibilities that an institution and an organization operating an IRB each will undertake to ensure compliance with the requirements of 45 CFR 46. For nonexempt HHS-supported research involving human subjects (or exempt research for which limited IRB review takes place) that takes place at more than one institution, Stanford and the other site shall document the institution's reliance on the selected IRB for oversight of the research and the responsibilities that each entity will undertake to ensure compliance with the requirements of this policy. Stanford utilizes the [SMART IRB agreement](#) and other written reliance agreements on a case-by-case basis.

Other IRB-Related Information

Other information is maintained by the Research Compliance Office, such as correspondence between the IRB and outside agencies and institutions, IRB convened meeting documentation - minutes, minutes lists, approval lists, agenda, and agenda lists, information about each IRB Member including; contact information, background and experience, curriculum vitae, etc. Documents are kept on the secure server and/or in eProtocol. The HRPP prepares and maintains adequate documentation of written procedures for the IRB as described in DHHS 45 CFR 46.108(a)(3) and (4).

8.2 Record Retention

The IRB maintains a complete set of materials relevant to the review of the research protocol or plan for a period of time sufficient to comply with legal and regulatory requirements, Sponsor requirements, and organizational policies and procedures. (AAHRPP Element II.5.A)

In accordance with the Common Rule and FDA regulations (45 CFR 46.115(b) and 21 CFR 56.115(b)), IRB records are retained for at least three years after the completion of the research, either electronically or as hard copy. In accordance with federal HIPAA privacy regulations, IRB records containing protected health information (PHI) are retained for at least six years after the completion of the research. It is Stanford policy to retain records for the greatest amount of mandated time. Thus, RCO retains and makes accessible all research records for at least six years. This policy applies to all research studies, whether or not participants were enrolled. Sponsored grants and contracts may require additional periods for record retention.

Records of VAPAHCS research are retained for 6 years as directed by the National Archives and Records Administration and delineated in the VHA's Records Control Schedule (RCS 10-1).

Other documents, such as meeting agendas and agenda lists and meeting minutes and minutes lists for the current IRB year are maintained in the office of the IRB Manager. Periodically, these documents are sent to an external vendor for long-term storage.

General correspondence from investigators and other documents not specific to a particular research protocol are maintained indefinitely in the RCO.

See Research Policy Handbook RPH 1.9 [Retention of and Access to Research Data](#) for Stanford University policy on record retention.

Maintenance of and Access to IRB Records

All hard copy IRB records of active protocols are secured in closed filing cabinets in locked buildings with regular security patrols and alarms. Records of closed protocols are sent to an external vendor for long-term storage. Access to those materials can be obtained in 48 hours, or less, if necessary.

The eProtocol system resides on a secured server, with password-protected access.

Access to IRB records is provided to the Vice Provost and Dean of Research, IRB Chairs, IRB members, IRB staff, and authorized VAPAHCS representatives (e.g., R&D Committee representatives) to carry out HRPP operations. Research investigators are provided reasonable access to files related to their own research.

All other Stanford access to IRB records is limited to those with a legitimate need for access, such as the Research Management Group, Office of Technology Licensing, Office of Sponsored Research, or Internal Audit. In addition, the RCO may allow access to IRB records by outside entities (e.g., monitors of sponsors of clinical trials) and agencies (e.g., regulatory agencies).

Research Policy Handbook RPH 18.4 [Confidentiality of Administrative Panel Proceedings](#) addresses the confidentiality of IRB meetings, meeting minutes, IRB Chairs' annual reports, research protocols and consent forms. The RCO will consider the IRB confidentiality policy and use its discretion and the reason for a request, to determine whether to grant access.

8.3 IRB Minutes

The IRB documents discussions and decisions on research studies and activities in accordance with legal and regulatory requirements, Sponsor requirements (if any), and organizational policies and procedures. (AAHRPP Element II.5.B)

The IRB or EC has and follows written policies and procedures to conduct reviews by the convened IRB: (AAHRPP Element II.2.E)

Element II.2.E.1. – Initial review

Element II.2.E.2. – Continuing review

Element II.2.E.3. – Review of proposed modifications to previously approved research

The IRB documents discussions, decisions, and findings either through the IRB minutes or for protocols subject to expedited review through documentation in the protocol file or other records.

The IRB minutes document:

- Meeting attendees and invitees
- Discussions and actions taken by the IRB and the separate deliberations for each action
- Determinations made by the IRB and the protocol-specific findings that justify those determinations
- Votes for each action recorded as numbers for, against, or abstaining
- Other issues requiring convened IRB review.

Attendance at an IRB Convened Meeting

Attendance at an IRB convened meeting is recorded in the minutes by documenting:

- The IRB members (voting, non-voting, and ex-officios) who are in attendance. Non-voting members include ex-officio members or alternate members attending for informational purposes
- The IRB members who are not in attendance
- When an alternate member replaces a primary member in attendance and voting at the convened meeting
- The continued presence of quorum for all votes, including a member whose primary concern is in a nonscientific area
- Attendance of members and alternate members who participate through videoconference or teleconference, and documentation that those members received all pertinent material before the meeting and had the opportunity to participate in all discussions actively and equally
- The IRB members who leave the meeting because of a conflicting interest
- The IRB members who leave the meeting briefly, are not present during a vote, and are not counted as part of the quorum
- The IRB members who arrive late or depart early from the meeting and their arrival or departure times
- The Research Compliance Office staff present
- Any others present (e.g., invited guests, investigators invited to address the IRB, and consultants)

Discussions and Actions Taken By the IRB

- Discussions and actions taken by the IRB, and the separate deliberations and basis for each action are documented in the minutes, such as:
- Discussion of protocol events – new, continuing review, modifications, reports of unanticipated problems and events and information requiring prompt review
- Approval of research – including the approval period for research, at initial and continuing review, (and if appropriate to the degree of risk determination of an approval period of less than one year)
- Approval of research contingent on specific minor conditions, and the designee (staff or panel member) appointed to sign off on the condition when met. If the condition is met after the minutes for that meeting are approved, the approval is documented in the minutes of the first IRB meeting that takes place after the contingency is met.

VA research:

The IRB Chair or an experienced IRB voting member designated by the Chair must sign off when conditions are met.

- Suspensions and terminations of previously approved research
- Disapproval of research
- Discussion of controverted issues and their resolution or disposition
- Requests for consultant review or input from an expert in the field (e.g., requests made during a convened meeting)
- Actions resulting from review of reports of unanticipated problems involving risks to participants or others, or other reportable events and information
- Actions resulting from determinations of serious or continuing non-compliance
- ***If a protocol is using a DHHS-approved sample consent:*** The justification of any deletion or substantive modification of information concerning risks or alternative procedures contained in the sample consent document

Determinations Made by the IRB

Determinations made by the IRB are recorded in the minutes or in the eProtocol application for expedited reviews with documentation of the protocol-specific findings justifying those determinations as appropriate, such as:

- Significant risk and non-significant risk device determinations, pursuant to:
 - 21 CFR 812.2(b), 21 CFR 812.150(b)(9)

- and considering [FDA Information Sheet](#)
- and [Significant Risk and Non-Significant Risk Medical Devices Studies](#) [GUI-7m]
- Approval of waiver or alteration of informed consent, pursuant to:
 - 45 CFR 46.116(e), 45 CFR 46.116(f) and [21 CFR 50.22](#)
- Waiver of informed consent documentation, pursuant to:
 - 45 CFR 46.117(c) and 21 CFR 56.109(c)(1)
- Research involving adults with impaired decision-making
- Waiver of HIPAA Authorization, pursuant to 45 CFR 164.512(i)(2)(ii)
- Waiver of HIPAA Authorization for recruitment or screening, pursuant to 45 CFR 164.512(i)(2)(ii)
- Alteration of HIPAA Authorization, pursuant to 45 CFR 164.512(i)(2)(ii)
- Use of short form process for consent:
 - 45 CFR 46.117(b)(2) or 21 CFR 50.27(b)(2)
- When research involves children, the following IRB decisions are documented:
 - Appropriate children finding applicable to research:
 - 45 CFR 46.404, 45 CFR 46.405, 45 CFR 46.406, 45 CFR 46.407, 45 CFR 46.408 (OHRP)
 - 21 CFR 50.51, 21 CFR 50.52, 21 CFR 50.53, 21 CFR 50.54, 21 CFR 50.55 (FDA)
 - Whether the permission of one parent/guardian is sufficient or if permission from both parents/guardians is recommended or required. (See guidance [Parental Permission](#) [GUI-C34])
 - The participation of children who are wards of the state is approved under:
 - 45 CFR 46.406, 45 CFR 46.407 only if 45 CFR 46.409(a) is satisfied, or
 - 21 CFR 50.53, 21 CFR 50.54 only if 21 CFR 50.56(a) is satisfied
- Appropriate involvement of pregnant women, fetuses, and neonates pursuant to:
 - 45 CFR 46.204, 45 CFR 46.205, 45 CFR 46.206, and 45 CFR 46.207
- Approval of research involving transplantation of fetal tissue:
 - 42 USC 498A(b)(1) and (2)

- Approval of research involving prisoners as participants under the following regulations:
 - 45 CFR 46.305 and 45 CFR 46.306
- Determination of the level of risk
- Determinations of serious or continuing non-compliance
- Unanticipated Problems and Unanticipated Adverse Device Effect
- Determinations of Suspensions or Terminations

Other Issues

Other issues are documented in the minutes, including but not limited to:

- Other events and information that require prompt reporting to the IRB (per guidance [Events and Information that Require Prompt Reporting to the IRB](#)[GUI-P13])
- Approval of minutes of prior convened IRB meetings
- The approval of research contingent on specific minor conditions by the chair or designee, in the minutes of the first IRB meeting that takes place after the date of the approval
- Presentation of information from an outside consultant or expert as previously requested by the IRB
- Special situations such as use of a test article and humanitarian use devices
- The names of IRB members who abstain for reasons other than conflict of interest
- Other items as applicable
- **For VA research:** Correspondence between the IRB and the Research & Development Committee

Disposition of the IRB Minutes

The IRB staff writes minutes and makes them available for IRB review one week before the next month's meeting. Minutes may not be altered by anyone including a higher authority once approved by the members at a subsequent IRB meeting.

The minutes of convened IRB meetings are considered confidential, and access to them is restricted and secured.

All IRB meeting minutes are made available to the Vice Provost and Dean of Research.

The IRB provide those portions of the minutes concerning VA research to the VA Palo Alto Health Care System (VAPAHCS) and follow [VHA Directive 1200.05](#) for VA IRB minutes.

Ch. 9: Risks to Research Participants

The IRB has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society. (AAHRPP Element II.3.A)

Definitions

Risk in the context of human subject research refers to the combination of the probability and magnitude of some future harm or injury (physical, psychological, social, or economic) occurring as a result of participation in a research study. Both the probability and magnitude of possible harm may vary independently and result in risks that range from "high" to "low" depending on whether they are more (or less) likely to occur, and whether the potential harm is more (or less) serious.

Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.” [45 CFR 46.102(j); FDA 21 CFR 56.102(i)]. For example, the risk of drawing a small amount of blood from a healthy individual for research purposes is no greater than the risk of doing so as part of routine physical examination.

Other definitions of risk or greater than minimal risk: Regulations, funding agency requirements or guidance applicable to specific situations or populations (e.g., prisoners, children) may refer to different definitions, including definitions of minimal risk. See [Other Federal Agencies - Additional Requirements](#) [GUI-42].

9.1 Steps to Minimizing Risk

The IRB has and follows written policies and procedures for identifying and analyzing risks and identifying measures to minimize such risks. The analysis of risk includes a determination that the risks to participants are reasonable in relation to the potential benefits to participants and to society. (AAHRPP Element II.3.A)

These policies and procedures are based on: Common Rule [45 CFR 46.111\(a\) \(1\),\(2\)](#); FDA [21 CFR 56.111\(a\)\(1\),\(2\)](#); [VHA Directive 1200.05](#).

When reviewing the protocol application submitted by the Protocol Director (PD), the IRB analyzes levels of risk, ensures risks are minimized, and ensures risks are reasonable relative to anticipated benefits, before approving the proposed research. (See [Chapter 14.3](#).)

Identifying Potential Risks (PD Input)

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The PD must describe in the Protocol Application:

- Potential risks to participants, including a scientific estimate of their frequency, severity, and reversibility.
- The statistical incidence of complication and the mortality rate of the proposed procedure, if known.
- The planned procedures for protecting against or minimizing potential risks, including risks to confidentiality. Two plans are necessary:
 - i. One to ensure necessary medical or professional intervention in the event of harm to participants
 - ii. One to ensure the safety of participants and the validity and integrity of research data. Data and safety monitoring must be commensurate with risks and the size and complexity of the trials. (See [Chapter 9.2](#) below).

When proposing changes to the research, PDs must submit a Modification form describing the proposed changes and explaining their impact on the level of risk and potential benefits.

Analyzing Levels of Risk (PD Input)

When PDs submit a regular new Protocol Application, Modification Form, or a Continuing Review Form, they must indicate the level of risk as being:

- **Low** – including, but not limited to, any minimal risk that does not fit under expedited categories 1-7 (e.g., innocuous procedures such as phlebotomy, urine or stool collection, no therapeutic agent, or safe therapeutic agent such as the use of an FDA approved drug or device)
- **Medium** – e.g., therapy with chemotherapy, antibodies, or a non-FDA approved potentially toxic drug, invasive procedures such as organ biopsies or catheter procedures, and some studies using biological agents
- **High** – e.g., novel therapeutic procedures, first-in-humans drug or device studies, some studies using biological agents or recombinant DNA vector studies

Ensuring Risks Are Minimized (IRB Determination)

The breadth of scientific disciplines represented by the IRB membership (see [Chapter 6](#)) allows for a critical assessment of research protocols. The IRB considers the overall level of risk to participants in evaluating the proposed research in accordance with the conditions outlined in 45 CFR 46.111(a)(1-7), 21 CFR 56.111(a)(1-7) and the ethical principles outlined in the Belmont Report. Furthermore, the IRB may consult with additional experts as needed. [45 CFR 46.111(a)(1)(i), 21 CFR 56.111 (a)(1)(i)]

Before approving a research protocol, the IRB must determine that risks are minimized as follows by:

- Ensuring that the proposed research has a sound research design
 - [45 CFR 46.111(a)(1)(i) , 21 CFR 56.111.(a)(1)(i)]
- The research does not expose subjects to unnecessary risks
 - [45 CFR 46.111(a)(1)(i) , 21 CFR 56.111.(a)(1)(i)] and
- Whenever appropriate, utilizing procedures that are already being performed on the subjects for diagnostic or treatment purposes
 - [45 CFR 46.111(a)(1)(ii), 21 CFR 56.111.(a)(1)(ii)].

The IRB examines the research plan, including research design and methodology, to determine that there are no inherent flaws that would place research participants at unnecessary risk. This includes the risk that research lacking in statistical power may not lead to meaningful results. Appropriate safeguards can also minimize risk to participants, for example: having an adequate data monitoring plan, or protecting confidentiality by using coded data. If risks are not adequately minimized, the protocol will not be approved as written. See guidance [Evaluating Sound Study Design](#) [GUI-17].

The IRB also considers the professional qualifications and resources (including time, equipment, support services) of the research team to protect participants and minimize potential harm. Research personnel must have received appropriate training, and clinicians involved in the research must maintain appropriate professional credentials and licensing privileges.

See [Chapter 14.5](#) and [Chapter 15.1](#).

Potential Risks v. Anticipated Benefits (PD Input)

The Protocol Application requires that the PD describe the potential benefit(s) that may be gained by participants, and how the knowledge gained may benefit the participants, future participants, or society. The PD must explain how these potential benefits to the participant or society outweigh the risks inherent in the research.

Potential Risks v. Anticipated Benefits (IRB Determination)

The IRB determines whether the risks of the research are reasonable in relation to the anticipated benefits (if any) to research participants and the importance of the knowledge that may reasonably be expected to result. [45 CFR 46.111(a)(2), 21 CFR 56.111(a)(2), 38 CFR 16.111(a)(2)]

The IRB bases its risk/benefit analysis on the information provided by the PD and by the expertise of its members and consultants who utilize the most current information about the risks and benefits of the interventions involved in the research.

The IRB considers only those risks that result from the research, and does not consider long-range effects (e.g., public policy implications) of applying the knowledge gained in the research.

The IRB does not consider those risks and benefits that participants would receive even if not participating in the research. [45 CFR 46.111(a)(2) and 21 CFR 56.111(a)(2)]

9.2 Data Monitoring Plan

The IRB has and follows written policies and procedures for reviewing the plans for data and safety monitoring, when applicable, and determines that the data and safety monitoring plan provides adequate protection for participants. (AAHRPP Element II.3.B)

To approve research, the IRB must determine that, where appropriate, the research plan makes adequate provisions for monitoring the data to ensure the safety of research participants. (45 CFR 46.111(a)(6), 21 CFR 56.111(a)(6), 38 CFR 16.111(a)(6))

Many studies (e.g., if more than minimal risk) need a Data and Safety Monitoring (DSM) Plan:

- The DSM Plan must be commensurate with the level of risk, size, and complexity of the study.
- The DSM Plan might need to include a DSMB or DMC (a data safety monitoring board, or committee – the terms are generally used interchangeably): for example, a DSMB or DMC may be required as part of the monitoring plan by NIH, FDA, other sponsors, or the IRB.

PDs are required to describe a Data Monitoring Plan, if applicable, in the Protocol Application.

See:

- Guidance [Data and Safety Monitoring](#) [GUI-P20] - for detailed information on what a data monitoring plan might address, when a data monitoring plan is required, and when a data monitoring board or committee is required.
- [Data Safety Monitoring Board \(DSMB*\) in Phase I/II Cell and Gene Transfer Clinical Trials](#) [AID-59]
- [Data Safety Monitoring Plans, and Data Monitoring Committees - Decision Chart](#) [GUI-P21]
- [Chapter 15.4](#) - discusses PD responsibilities
- VA requirements [VHA Directive 1200.05](#)
- Data Monitoring Committees - FDA March 2006 “[Guidance for Clinical Trial Sponsors](#)”
- Data Monitoring Plans and Data Monitoring Committees – NIH and NCI policies:
 - [NIH: Policy for Data and Safety Monitoring](#)
 - [NIH: Further Guidance on Data and Safety Monitoring for Phase I and Phase II Trials](#)

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- [NCI: Data and Safety Monitoring Guidelines](#)

Additional Requirements

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

IRB Review of the Data Monitoring Plan

The IRB primary reviewer reviews the proposed Data Monitoring Plan, and the administration and composition of the monitoring entity, when applicable. If additional expertise is needed, the IRB will seek input from persons with appropriate knowledge.

Continuing Review; Timeframe for Reporting Data Monitoring Findings to the IRB

It is not the role of the IRB to perform data monitoring, but to ensure that appropriate monitoring is taking place, and to review reports from the monitoring entity.

The IRB must ensure that the conditions satisfied in order for initial IRB approval of the research are still satisfied at continuing review, as applicable. These include, but are not limited to, determinations by the IRB regarding risks, potential benefits, informed consent, and safeguards for participants. Thus, the PD must include in the continuing review application the outcomes of data and safety monitoring including a summary of adverse events, any unanticipated problems, and any new information pertaining to the research - either from the research itself or from other sources, which have occurred since the previous IRB review. The amount of detail required depends on the type of research being conducted. In many cases, an appropriate summary would be a simple brief statement that there have been no unanticipated problems and that adverse events have occurred at the expected frequency and level of severity as documented in the research protocol, the informed consent document, and any investigator brochure.

In addition, periodic (usually annual) reports from the monitoring entity are submitted by the PD to the IRB at continuing review. (When a monitoring entity is used, the IRB conducting continuing review of the research may choose to rely on a current statement from the monitoring entity indicating that it has and will continue to review study-wide adverse events, interim findings, and any recent literature that may be relevant to the research.)

Whether the method of monitoring is by PD oversight or from the establishment of a DSMB, the IRB can tailor a specific timeframe for future reporting of data monitoring findings to the IRB. The IRB can set the date of continuing review for the protocol as being less than the maximum of a year, if they determine that interim reporting of data monitoring information will serve to better protect participants. Alternatively, the IRB can request a report after a specific number of participants are enrolled or after a serious adverse event has been reported.

9.3 Risks to Special Populations

The IRB has and follows written policies and procedures for determining the risks to prospective participants who are vulnerable to coercion or undue influence and ensuring that additional protections are provided as required by applicable laws, regulations, codes, and guidance. (AAHRPP Element II.4.A)

The IRB is cognizant of the vulnerable nature of many participants. Food and Drug Administration (FDA) regulations and the Common Rule require IRBs to give special consideration to protecting the welfare of vulnerable participants.

In order to approve research involving vulnerable populations, the IRB must determine, where appropriate, that additional safeguards have been included to protect the rights and welfare of participants who are likely to be vulnerable to coercion or undue influence, such as:

- Children (45 CFR 46 Subpart D; 21 CFR 50 Subpart D),
- Prisoners (45 CFR 46 Subpart C),
- Persons with mental disabilities, or
- Economically or educationally disadvantaged persons

Additional Requirements

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy, and the Environmental Protection Agency): See [Other Federal Agencies - Additional Requirements](#) [GUI-42].

The IRB includes among its members persons who are knowledgeable about and experienced in working with vulnerable participants. (45 CFR 46.107(a); 21 CFR 56.107(a)). When a research study involves a vulnerable population not otherwise covered by these policies, the IRB takes steps to evaluate whether additional safeguards have been included in the research to protect the rights and welfare of participants.

See also [Chapter 12.2](#) for consent procedures for vulnerable populations.

Considerations in Reviewing Research Involving Vulnerable Participants

The IRB considers the following elements of the research plan when reviewing research involving vulnerable participants:

- **Strategic issues** that involve inclusion and exclusion criteria for selecting and recruiting participants; informed consent and willingness to volunteer; coercion and undue influence; and confidentiality of data.
- **Group characteristics**, such as economic, social, physical, and environmental conditions, to ensure that the research incorporates additional safeguards for vulnerable participants.

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- **Participant selection to prevent over-selection or exclusion** of certain participants based on perceived limitations or complexities associated with those participants. For example, it is not appropriate to target prisoners as research participants merely because they are a readily available “captive” population.
- **Application of state or local laws** that bear on the decision-making abilities of potentially vulnerable populations. State statutes (as discussed in [Chapter 12](#)) often address issues related to competency to consent for research, emancipated minors, legally authorized representatives, the age of majority for research consent, and the waiver of parental permission for research.
- **Procedures** for assessing and ensuring participants’ capacity, understanding, and informed consent or assent. When weighing the decision whether to approve or disapprove research involving vulnerable participants, the IRB verifies that such procedures are a part of the research plan. In certain instances, it may be possible for investigators to enhance understanding for potentially vulnerable participants. Examples include requiring someone not involved in the research to obtain the consent, the inclusion of a consent monitor, a participant advocate, interpreter for hearing-impaired participants, translation of informed consent forms into languages the participants understand, and reading the consent form to participants slowly and ensuring their understanding paragraph by paragraph.
- **Need for additional safeguards** to protect potentially vulnerable populations. For example, the IRB may require that the investigator submit each signed informed consent form to the IRB, that someone from the IRB oversee the consent process, or that a waiting period be established between initial contact and enrollment to allow time for family discussion and questions.

For information on the recruitment of vulnerable populations see:

- [Observation of the Consenting Process](#)
- Guidance [Recruitment](#) [GUI-33]
- Human Subjects Research [website](#)
- [Chapter 14.4](#)

Children

Children: Under the regulations, children are persons who have not attained the legal age for consent to treatments or procedures involved in the research under the applicable jurisdiction in which the research will be conducted.

The IRB follows the requirements of the DHHS regulations at 45 CFR 46, Subpart D and FDA regulations at 21 CFR Part 50, Subpart D in reviewing protocols involving children. The IRB makes the findings and determinations required by the DHHS and FDA regulations related to the risks before allowing research involving children to proceed.

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When the IRB makes a finding that 45 CFR 46.407 or 21 CFR 50.54 apply, the IRB must refer the protocol to the appropriate agency for review and approval. For studies regulated by OHRP, the proposed activity is referred to the Secretary of HHS. For studies regulated by the FDA, the proposed activity is referred to the FDA’s Office of Pediatric Therapeutics for public review and approval.

See guidances:

- [Additional Protections for Inclusion of Children in Research \(OHRP\)](#)
- [Additional Safeguards for Children in Clinical Investigations \(FDA\)](#)
- [Parental Permission](#) [GUI-C34]
- [Chapter 12.2](#) for consent requirements for research involving children participants.

VA Research Involving Children

Research involving children must not present greater than minimal risk to the children and should only be conducted by VA investigators while on official duty or at VA or approved off-site facilities if permission has been granted by the Local Medical Center Director. If the permission is granted, the research must be in accordance with applicable Federal regulations pertaining to children as research subjects (see 45 CFR Part 46, Subpart D 46.401 – 46.404 and 46.408). See [VHA Directive 1200.05](#).

Prisoners

Prisoner: Any individual involuntarily confined or detained in a penal institution. This includes individuals:

- sentenced to such an institution under a criminal or civil statute,
- detained in other facilities by virtue of statutes or commitment procedures which provide alternatives to criminal prosecution or incarceration in a penal institution,
- detained pending arraignment, trial, or sentencing.

DHHS details special protections for research involving prisoners, who due to their incarceration may have a limited ability to make truly voluntary and un-coerced decisions about whether or not to participate as participants in research.

[45 CFR 46, Subpart C]. The IRB will apply the standards of Subpart C to all prisoner research, whether or not DHHS-supported.

DHHS-supported research: The IRB must certify to the Secretary (of DHHS), via the Office for Human Research Protections (OHRP) that it has reviewed and approved the research under 45 CFR 46.305; additionally, the Secretary (through OHRP) must determine that the proposed research falls within permissible categories [45 CFR 46.306(a)(2)].

If biomedical or behavioral research is conducted or supported by DHHS, approval must be obtained from the Secretary of DHHS (through OHRP) before commencing research.

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Note: OHRP discourages expedited review of any research involving prisoners as participants.

Non-DHHS-supported research: Certification to OHRP is not required; the IRB substitutes a comparable risk assessment measure in place of the review and approval by the Secretary of DHHS.

Refer to guidance [Involvement of Prisoners in Research](#) [GUI-10] for:

- Special requirements regarding IRB composition and additional duties
- Categories of permissible research
- Other requirements pertaining to DHHS-supported research
- IRB required findings.

In order to consider research involving prisoners, the IRBs must:

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

When a previously enrolled research subject becomes a prisoner, and the relevant research protocol was not reviewed and approved by the IRB (under 45 CFR 46, Subpart C) the PD should promptly notify the IRB of this event through the IRB Report Form. The PD should state that all research interactions and interventions with, and obtaining identifiable private information about, the now-incarcerated prisoner-participant will cease until the requirements of Subpart C have been satisfied with respect to the relevant protocol, unless the PD asserts that it is in the best interests of the participant to remain in the research study while incarcerated, in which case the IRB Chair may determine that the participant may continue to participate in the research until the requirements of Subpart C are satisfied. Upon receipt of notification that a previously enrolled research participant has become a prisoner, the IRB should promptly re-review the protocol in accordance with the requirements of Subpart C if the PD wishes to have the prisoner participant continue to participate in the research.

Research Involving Prisoners in California

If the research involves prisoners in a California facility, the IRB must comply with the additional limitations and requirements in California Penal Code Sections 3501 - 3523. Those provisions limit the types of biomedical research that may be conducted and place additional requirements on other types of research. Guidance [Research Involving Prisoners – California Penal Code: Section 3501 – 3523](#) [GUI-38] is referred to when the IRB reviews a protocol involving prisoners in California facilities.

DHHS Conducted or Supported Epidemiologic Research Involving Prisoners as Subjects

Under certain conditions DHHS conducted or supported epidemiologic research may be approvable by the Secretary of DHHS, as outlined in the [Federal Register Vol 68 No.119, June 20, 2003](#).

VA Research Involving Prisoners

Research involving prisoners must not be conducted by VA investigators while on official duty, or at VA-approved off-site facilities unless a waiver has been granted by the Chief Research and Development Officer (CRADO). If the waiver is granted, the research must be in accordance with applicable Federal regulations pertaining to prisoners as research subjects (45 CFR Part 46, Subpart C 46.301 – 46.306).

See [VHA Directive 1200.05](#) or the VA research website for requirements for requesting a waiver.

Individuals with Impaired Decision-making Capacity

The IRB reviews the risk-benefit analysis including the possibilities of coercion and undue influence and must determine whether such participants should be recruited and whether support mechanisms, such as surrogate consent, are appropriate. See [Chapter 12.2](#) for more information on the consent process, and criteria for including individuals with impaired decision-making capacity in research.

Pregnant Women, Human Fetuses, and Neonates

The Department of Health and Human Services (DHHS) details special protections for research involving pregnant women, human fetuses, and neonates. [[45 CFR 46, Subpart B](#).]

Under these regulations, the IRB is required to document specific findings to minimize the potential for risk or harm to the fetus, and additional attention must be given to the conditions for obtaining informed consent, in accordance with the guidance [Research Involving Pregnant Women, Fetuses, and Neonates](#)[GUI-8].

In general, Subpart B requires that research involving pregnant women, human fetuses, and neonates should involve the least possible risk. Persons engaged in the research may have no part in the timing, method, or procedures used to terminate the pregnancy, or to determine the viability of the fetus. No inducements may be offered to terminate a pregnancy.

Four separate conditions, each with their own requirements and IRB determinations, apply to research with pregnant women, human fetuses, and neonates:

1. **Research Involving Pregnant Women.** No pregnant women may be involved as a participant in research unless either of the following conditions applies: The purpose of the activity is to meet the health needs of the mother, and the fetus is placed at

risk only to the minimum extent necessary to meet such needs; **OR** the risk to the fetus is minimal. The mother and the father must be legally competent and provide consent, unless the purpose of the research is to meet the health needs of the mother, or the father is not reasonably available, or the pregnancy resulted from rape.

2. **Research Directed at Human Fetuses.** The IRB must find that: the purpose of the research is to meet the health needs of the individual fetus and shall be conducted in a way that will minimize risk; **OR** the research will pose no more than minimal risk to the fetus, and the purpose of the activity is to ascertain important biomedical knowledge that is unobtainable by other means. These activities are permitted only if the mother and father are legally competent and have given their informed consent, unless the father is not reasonably available, or the pregnancy resulted from rape.
3. **Research Involving Neonates.** For research involving neonates, the IRB must distinguish between viable and non-viable neonates. Viable is defined in the regulations as being able to survive to the point of independently maintaining a heartbeat and respiration, given the benefit of available medical therapy. If the neonate is viable, it is considered a “child” and may be involved in research to the extent permissible under 45 CFR 46, Subpart D, which is discussed later in this chapter.
 - **A non-viable neonate** may not be involved in research unless all of the following conditions apply: The vital functions of the neonate are not artificially maintained; experimental activities that would of themselves terminate the heartbeat or respiration are not employed; AND the purpose of the research is development of important biomedical knowledge that cannot be obtained by other means. Research involving a non-viable neonate is permitted only when both parents have given their informed consent, unless one parent is not reasonably available, or the pregnancy resulted from rape or incest. In the case of non-viable neonates, consent by a parent’s legally authorized representative is not allowed.
 - **A neonate of uncertain viability** may not be involved in research unless one of the following conditions applies: There is no added risk to the neonate and the purpose of the research is to obtain important biological knowledge that cannot be obtained by other means; OR the purpose of the activity is to enhance the probability of survival of the individual neonate. Research involving a neonate of uncertain viability is permitted only if either parent or the parent’s legally authorized representative gives their permission.

Non-Pregnant Women of Reproductive Potential

Unilateral exclusion of non-pregnant women of reproductive potential from research is not permitted by the IRB. Exclusion requires compelling scientific justification. Where such justification exists, it may also be appropriate to exclude men of reproductive potential.

VA Research – special requirements

- **Pregnant Women:** See [VHA Directive 1200.05](#) for specific requirements.

Other Potentially Vulnerable Participants

The context of the research is an important consideration for the IRB when reviewing research that involves other potentially vulnerable participants such as research involving persons experiencing homelessness, members of particular minority groups, or the economically or educationally disadvantaged. Research involving significant follow-up procedures or offering significant monetary compensation may unduly influence certain types of participants and the IRB takes such considerations into account. Nevertheless, research involving these participants is socially important for understanding and eventually improving adverse health and general well-being in these populations.

Employees and Students

Employees, lab personnel, students, and trainees at Stanford and other facilities under the purview of the IRB are considered vulnerable participants, in particular because of the risk of coercion and undue influence. The IRB has the same standards for approving research involving these groups as other vulnerable participants.

9.4 Suspension or Termination of IRB approval

The IRB has and follows written policies and procedures for suspending or terminating IRB approval of research, if warranted, and for reporting these actions, when appropriate. (AAHRPP Element II.2.H)

Definitions

Suspension: Temporary withdrawal of IRB approval for some or all research procedures in a protocol or the permanent withdrawal of IRB approval of part of a protocol. Continuing review of the research is still required as specified by the IRB. A sponsor-imposed suspension alone does not constitute such a suspension, as it is not an action by the IRB to withdraw approval of a previously approved protocol. Similarly, an action by the Protocol Director (PD) that halts or materially changes some or all of the PD's protocol as previously approved by the IRB does not constitute such a suspension (but may need to be submitted to the IRB as a protocol modification).

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Termination: Permanent withdrawal of IRB approval of a previously approved protocol. Continuing review of the research is still required as specified by the IRB.

Suspension or Termination by the Convened IRB

The IRBs have the authority (45 CFR 46.113; 21 CFR 56.113) to suspend or terminate a previously approved non-exempt protocol or exempt protocol under limited IRB review (i.e., both from the approval of this policy by the Vice Provost and Dean of Research and through the [charge](#) to IRB Chairs and members at the time of their appointment.)

The IRB may act to suspend or terminate a protocol for any of the following reasons including but not limited to:

- Not conducting research in accordance with IRB requirements
- Unexpected serious harm to subjects.

The IRB Chair shall:

- Notify the PD in writing of it the IRB decision to suspend or terminate its approval along with a statement of the reasons for the IRB action and any terms and conditions of any suspension.
- Report the decision to suspend or terminate to the Vice Provost and Dean of Research and others in accordance with the procedure set forth in [Chapter 3.9](#).

The PD shall be provided with an opportunity to respond in person or in writing to the IRB on a suspension or termination.

If the IRB action in relation to the suspension or termination involves the withdrawal or modification of participation of current participants from the research, the IRB shall direct the PD to contact the participants to:

- Make such notification with an explanation, after its review and approval by the IRB
- Describe any monitoring and follow-up for safety reasons that will be conducted
- Provide contact information for the PD and the IRB where the participant may report any adverse events or unanticipated problems.

Suspension or Termination by an Authorized Individual

The following Stanford officials are authorized to suspend or terminate IRB approval pending review by the IRB responsible for continuing review of the protocol: the Vice Provost and Dean of Research, the Chair of the IRB responsible for continuing review of the protocol, the Director of Research Compliance, and any other Stanford official who is authorized to take such action by virtue of his or her office or of a policy or procedure of the relevant Stanford organization. The Stanford official who makes a suspension of a protocol shall immediately:

- Notify the PD: (i) to halt the portion of the IRB approved protocol that poses immediate, material risk to participant health and welfare, (ii) of the reasons for the

suspension or termination, and (iii) of the opportunity to respond in person or in writing to the official and IRB on the suspension or termination

- Report the suspension or termination and its basis to the IRB.

The IRB staff shall:

- Report the suspension or termination as a “suspension or termination of IRB approval” to the Vice Provost and Dean of Research and others in accordance with the procedure set forth in [Chapter 3.9](#)
- Immediately initiate the appropriate procedure for review of the basis for the suspension or termination (e.g., the procedure for reviewing possible non-compliance or a possible unanticipated problem. See [Chapter 3.9](#), [3.10](#)).

If the halt in some or all of the protocol involves the withdrawal from the research or modification of participation of current participants, the official or IRB shall direct the PD to contact the participants to:

- Make such notification with an explanation, after its review and approval by the IRB
- Describe any monitoring and follow-up for safety reasons that will be conducted
- Provide contact information for the PD and the IRB where the participant may report any adverse events or unanticipated problems.

Protection of Participants Who May Be Affected by the IRB Action

If the suspension or termination will affect participants in the protocol (e.g., requires withdrawal of participants), the IRB shall utilize a process that takes into account the impact on their health and safety. This should occur before the suspension or termination, when it is feasible, and delay will not jeopardize their health and safety. Examples include:

- Requiring the PD to submit proposed procedures for any withdrawal of participants
- Allowing participants to continue (e.g., treatment with an investigational drug) if the IRB determines that it is in their best interests
- Requiring submittal for review and approval of the IRB or its designee of all communications by the PD to participants about the IRB action
- Designating an investigator other than the PD to be responsible for carrying out the IRB decision
- Requiring the appointment of a new PD or transferring responsibility for participants to another investigator
- Requiring the PD to carry out follow-up or monitoring of participants appropriate to the circumstances (e.g., for any adverse impact on participants after suspension or termination)

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- Requiring special reporting (e.g., adverse events or outcomes) concerning participants by the PD.

VA Research

Once notified of the suspension, the investigator must immediately submit to the IRB Chair, a list of research subjects for whom suspension of the research would cause harm. The IRB Chair, with appropriate consultation with the VA Chief of Staff, determines if the subject may continue in the research.

IRBs of academic affiliates that are the IRB of record for a VA facility must follow these requirements. The IRB must notify the VA medical facility Director, the RCO, and the ACOS/R&D in writing within five (5) business days of becoming aware of any of the following: The suspension or early termination of a non-exempt VA human research study by the IRB or Organizational Official due to the study not being conducted in accordance with applicable regulations, policies, agreements, or IRB requirements or due to concerns about the safety, rights, or welfare of human participants or others, if such suspension or termination is not otherwise reportable per the requirements of paragraphs 7a, b, or c of VHA Directive 1058.01. The notification of suspension or early termination of a non-exempt VA human research study by the IRB or Organizational Official must include a statement of the reason for the IRB's or Organizational Official's action. See [VHA Directive 1058.01](#) for additional procedures and reporting requirements for suspension or termination of IRB approval for VA research.

Ch. 10: Participant Recruitment and Selection

10.1 Equitable Selection

The IRB has and follows written policies and procedures to evaluate the equitable selection of participants. (AAHRPP Element II.3.C)

Guidance and information are made available to Protocol Directors (PDs) to assist and guide them in creating recruitment and participant selection methods that are fair and equitable. See:

- [Recruitment](#) [GUI-33]
- [Advertisements: Appropriate Language for Recruitment Material](#) [GUI-16]
- [Chapter 14.4](#)

PDs are directed to enter detailed information on how participants will be identified and recruited in response to questions in the Protocol Application. PDs are required to identify the target populations (including age range, gender, and ethnic background), the inclusion and exclusion criteria and whether payments will be made for participation. In addition, PDs are required to justify the inclusion of targeted persons (e.g., healthy participants, employees, students, or participants with certain medical conditions). In determining if the selection and recruitment of participants is equitable, the IRB takes into account the purpose of the research, the setting in which the research will be conducted, whether prospective participants will be vulnerable to coercion or undue influence, the selection (inclusion/exclusion) criteria, participant recruitment and enrollment procedures, and the influence of payments to participants. The IRB also evaluates whether the study imposes fair and equitable burdens and benefits - such that one group of persons does not disproportionately receive the benefits compared to another group assuming only the risks.

IRB staff and members review this information and confirm the recruitment and selection strategies are fair, equitable, and not misleading. If recruitment strategies fail to meet these requirements, the protocol will not be approved as written and the PD will be asked to modify the recruitment plan accordingly, as a condition of approval. VA studies follow [VHA Directive 1200.05](#).

Vulnerable Subjects

Investigators must provide a rationale for involvement of vulnerable subjects, such as children, prisoners, economically and educationally disadvantaged, individuals with impaired decision-making capacity, and people experiencing homelessness. The PD must substantiate his/her decision to involve a vulnerable population and further provide a rationale why a less vulnerable population would not serve the purpose of the research. When vulnerable populations will be targeted for enrollment, the IRB assesses the additional safeguards proposed by the PD to minimize the possible risks and the chance of harm to these populations.

Non-English Speaking Participants

Non-English speaking participants should not be systematically excluded because of language barriers. The IRB encourages the inclusion of non-English speaking participants and permits such persons to be enrolled via the short form consent process consistent with 45 CFR 46.117(b)(2) and 21 CFR 50.27(b)(2). See Non-English [Speaking](#) Research Participant [GUI-03H23]

10.2 Review of Recruitment Methods, Advertising Materials and Payment

The IRB has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate. (AAHRPP Element II.3.C.1)

Recruitment Methods

PDs are required to provide details on all methods of recruitment proposed on a project, including how participants will be identified for recruitment. Guidance on recruitment is available, as well as sample phone screens when screening will be conducted over the phone to determine study eligibility. Some common recruitment methods include recruiting from one's own patients, seeking referrals from colleagues (via word of mouth or referral letters sent to colleagues) and advertisements.

Advertisements

The IRB considers that advertisements begin the informed consent process and thus, consistent with the consent process, coercion and undue influence are prohibited during recruitment. If recruitment will be by advertisement, the mode of advertisement (flyers, radio, newspaper, or internet) and information contained in the advertisement must be approved by the IRB.

- *Audio and video tape:* The IRB may review and approve the wording prior to taping in order to preclude re-taping due to inappropriate wording. The IRB reviews the final version of the advertisement.
- *Printed advertisement:* The IRB reviews the final copy.

See:

- [Recruitment](#) [GUI-33]
- [Advertisements: Appropriate Language for Recruitment Material](#)
- [Recruiting Study Subjects](#) [FDA]

Telephone Screening

For protocols involving telephone screening of participants in response to an advertisement, the IRB generally requires investigators to review all the required elements of informed consent

orally with prospective participants. However, investigators may request a waiver of documentation of consent limited to the screening portion (only) of the protocol if they demonstrate that the screening procedure meets regulatory criteria in 45 CFR 46.117(c)(1) (ii) or 21 CFR 56.109(c)(1).

Payment

PDs must disclose any proposed payments to participants in the protocol application form, including the method, type, and timing of the payments. Payments to research participants may not be of such an amount as to result in coercion or undue influence on the research participant's decision to participate. If a study has multiple paid visits, payment should be prorated throughout the duration of the study to provide partial payment to persons who withdraw before completing the study. See [Payment – Ethical Considerations](#) [GUI-39].

Prohibited Recruitment and Payment Practices

The following activities are examined carefully and are generally not allowed:

- Payment from research participants
- Compensation for participation in the form of a coupon for a discount on the test article to be used after the product has been approved for marketing.
- Exculpatory language through which the participant or participant's LAR is made to waive or appear to waive any of the participant's legal rights, or releases or appears to release the investigator, the sponsor, the institution, or its agents from liability for negligence.

Payment Arrangement among Sponsors/Organizations, Investigators and Others

Payment in exchange for referrals of potential participants (finder's fees) and payments designed to accelerate recruitment tied to the rate or timing of enrollment (bonus payment) are generally unacceptable.

In some special circumstances Stanford contracts with organizations for a fee who have volunteer participants who have previously agreed to be study participants in survey studies.

Payment Practices – Additional Requirements

Other Federally-Funded Research:

Additional requirements might apply, (such as payment and compensation limits, minimizing undue influence, etc.), depending on the source of support/funding (e.g., Department of Defense, Department of the Navy, Department of Justice): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

Ch. 11: Privacy and Confidentiality

Stanford has established the following written policies, together with the other policies referenced in this Chapter, to protect participant privacy and data confidentiality.

In order to approve research, the IRB must be satisfied that, “when appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of the data” [45 CFR 46.111(a)(7) and 21 CFR 56.111(a)(7)]. An invasion of privacy or breach of confidentiality may be a moral wrong or even present a risk of serious harm to participants (e.g., jeopardize their family relationships, community standing, employment, or lead to prosecution for criminal behavior). The IRB reviews each protocol, based on the information provided by the PD in the Protocol Application, and assesses the amount and type of private information involved, how the information will be collected, and plans for its use, storage, and disclosure. As necessary, the IRB will ask for additional details during its review.

Definitions

Privacy means, in the context of a research protocol, respecting an individual’s right to be free from unauthorized or unreasonable intrusion, including control over the extent, timing and circumstances of obtaining personal information from or about them. For example, individuals may not want to be seen entering a place that might stigmatize them, such as a clearly identified pregnancy counseling center.

Confidentiality means respecting a potential or current participant’s right to be free from unauthorized release of information that the individual has disclosed in a relationship of trust and with the expectation that it will not be divulged to others without permission in ways that are inconsistent with the understanding of the original disclosure. In the context of a research protocol, “confidentiality” refers to the understanding between the participant and investigator (e.g., as set forth in the consent and authorization documents) as to how participant information will be handled, managed, and disseminated (e.g., shared with others) as part of the research.

Private Information means individually identifiable information:

- About behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place
- 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).

Sensitive Information is private information relating, but not limited, to:

- Sexual attitudes, preferences, or practices
- Use or treatment for alcohol, drugs, or other addictive products

- Illegal conduct
- Information which if released could reasonably cause stigmatization or discrimination, or result in damage to areas such as financial well-being, employability, or reputation.
- Certain health information, including psychological or mental health.

Protected Health Information (PHI) is defined in the [HIPAA privacy](#) regulations in [45 CFR 164.501](#) and in the Stanford University HIPAA policies.

Stanford Affiliated Covered Entity (SACE) means the portions of Stanford University designated as a part of the Stanford University HIPAA Components (SUHC) hybrid covered entity (e.g., its health care components and selected support units) joined with the Stanford Hospital and Clinics (SHC) and Lucile Packard Children's Hospital (LPCH), to form a single affiliated entity as a covered entity under the HIPAA privacy regulations.

11.1 Protecting the Privacy of Participants

The IRB has and follows written policies and procedures to evaluate the proposed arrangements for protecting the privacy interests of research participants, when appropriate, during their involvement in the research. (AAHRPP Element II.3.D)

Privacy refers to persons and their interest in controlling the access of others to themselves.

To approve research, the IRB must determine that, where appropriate, there are adequate provisions to protect the privacy interests of potential or current participants, from the screening and recruitment through all phases of research. If the protocol does not include adequate provisions to protect the privacy interests of the participants, the IRB may not approve the protocol as written.

The PD must describe in the Protocol Application the provisions for protecting the privacy of participants during screening, data collection and other interactions. The IRB assesses the information during the review process and at convened meetings. As necessary, the IRB will ask for additional details during its review.

Provisions for protecting the privacy interests of participants or participants should include:

- Ensuring that the conditions under which a procedure is performed, or information is collected (e.g., physical locations, videoconferencing, telephone contact, mail, or email solicitations) afford protections against interactions with participants being witnessed, overheard, or inadvertently intercepted or viewed. For example, a potential or current participant may feel uncomfortable:
 - Being seen entering a place that they feel might stigmatize them, such as a pregnancy counseling center;
 - Having physical measurements recorded in a non-private setting;

- Discussing private medical information in a setting with other than a health care provider or in other than a private clinical setting;
- Answering sensitive questions by telephone while at home or work.
- Limiting the information being collected to only the minimum amount of data necessary to accomplish the research purposes.

11.2 Protecting the Confidentiality of Participant Information

The IRB has and follows written policies and procedures to evaluate proposed arrangements for maintaining the confidentiality of identifiable data, when appropriate, preliminary to the research, during the research, and after the conclusion of the research. (AAHRPP Element II.3.E)

Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to Stanford policies and procedures and to the requirements or determinations of the IRB. (AAHRPP Element III.2.C)

Confidentiality refers to maintenance of the Researcher's agreement with the participant about how the participant's identifiable private information will be handled, managed, and disseminated.

As a condition of protocol approval, the IRB determines that there are adequate provisions to protect confidentiality of information related to potential or current participants, throughout the research, including data analysis and retention. PDs are expected to design studies to maximize confidentiality to avoid unintentional and unauthorized release or other disclosures.

Additional Requirements

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Education (re: access to instructional material used in a research or experimentation program), Department of Energy (such as a required checklist for DOE requirements), Department of Justice: National Institute of Justice (NIJ) and research conducted with the Bureau of Prisons): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

The PD must describe the provisions to protect the confidentiality of data in the Protocol Application. The IRB assesses the information provided in the application during the review process and at convened meetings. The IRB may ask for additional details during its review, depending on the sensitivity of the information being used, maintained, or disclosed. Generally, the greater the sensitivity of the information, the more stringent the security measures that are needed.

In reviewing confidentiality protections, the IRB considers the nature, probability, and magnitude of harms that would be likely to result from an unauthorized release of the collected information. It evaluates the proposed anonymizing techniques, (e.g., de-identification, coding), storage plans, access restrictions, data security methods (e.g., encryption) and other relevant factors in making its final determination concerning the appropriateness and adequacy

of confidentiality protections. See the Protocol Application for the information requested by the IRB for this assessment.

For active protocols, any changes in confidentiality protection measures must be described in either a protocol modification or continuing review application. Such changes are reviewed according to the requirements described above for new protocols.

The IRB requires that investigators use best practices and adhere to Stanford security policies to protect the confidentiality of the information collected under a protocol.

Stanford University has guidelines for best practices for maintaining confidentiality. See the [Stanford University HIPAA privacy policies](#) including best practices for:

- Protecting PHI against public viewing;
- Storage and disposal of documents that contain PHI;
- Safeguarding computer workstations and databases that access PHI;
- Faxing and emailing PHI

Techniques described in these policies may be generally applied to all information.

The IRB may consult with the School of Medicine Office of Information Resources and Technology (IRT) or other Stanford security specialists if needed.

PDs must also follow Stanford security policies, as applicable to their respective departments or units, which define requirements for securing information maintained in electronic form. See:

- [Stanford University security policies: Information Security Office](#)
 - [Stanford Data Classifications chart](#) for definitions, examples, and handling requirements for prohibited, restricted, confidential, and public data
- [Stanford University HIPAA security policies](#)
- VAPAHCS security policies ([VHA Directive 1200.05](#); VHA Directive [6500](#))

Legally Required Release of Private Information

The IRB identifies protocols that might collect information that could be subject to a legally mandated release of information, to the extent that this can be ascertained in advance. When such protocols are identified in advance, the IRB requires that the investigator notify the participants through language in the consent and HIPAA authorization document(s) of the possibility of legally mandated disclosure. Examples of reportable information include:

- Child abuse reporting, California Penal Code 11169 – 11174.3;
- Elder and dependent adult abuse reporting, California Welfare and Institutions Code 15600 – 15659;
- Sexual assault and rape reporting, California Penal Code 11160;

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- Warning to police or potential victim when an individual is deemed a danger to others, California Welfare and Institutions Code 5328(r) and Tarasoff v. Regents of Uni. of CA, 17 Cal.3d 425 (1976);
- Reporting treatment of person suffering from assaultive or abusive behavior, California Penal Code 11160 – 11161;
- Reporting certain communicable diseases, California Health and Safety Code 120250 and 17 California Code of Regulations 2505;
- Reporting cases of active TB, California Health and Safety Code 121362;
- Reporting disorders characterized by a lapse of consciousness, 17 California Code of Regulations 2810;
- Reporting incidents involving medical devices, 21 USC 360i(b), 21 CFR Part 803.
- Release under a search warrant or a subpoena (e.g., civil or criminal litigation).

PDs may seek advice from the IRB or the relevant Stanford legal counsel, if they have any questions concerning compliance with these laws.

Certificates of Confidentiality (CoC)

Where a protocol involves the collection of sensitive information (e.g., about illegal conduct), the IRB may determine that special steps are needed to protect participants from the risks of external investigative or judicial processes (legally mandated release of information for use in federal, state, or local civil, criminal, administrative, legislative, or other legal proceedings). In such situations, the IRB may require that the PD obtain a Department of Health and Human Services (DHHS) Certificate of Confidentiality (CoC) pursuant to Section 241(d) of Title 42 of the United States Code. Funding through DHHS or other federal funding is not a requirement for obtaining a CoC.

NIH-funded biomedical research studies collecting identifiable or potentially identifiable information (e.g., linked or coded information), or generating individual-level genetic information, are automatically issued a Certificate of Confidentiality (CoC) as a condition of award.

When the PD obtains a CoC, or one is automatically issued for an NIH-funded study, the IRB requires that participants be informed about the protections and limitations under the CoC, through the consent document or HIPAA authorization. The consent document must explain if the investigators will release information under any anticipated mandatory reporting or for internal or external audit purposes (e.g., Stanford units, DHHS, or FDA). In order that a participant may weigh the risk of such release of information and not expect more confidentiality protection than is actually provided by the CoC, the IRB requires that the possibility of release for those purposes be stated clearly and explicitly in both the protocol and the consent form. The IRB also requires that any participant enrolled after expiration or

termination of a CoC be informed that its protection will not apply to them, and that issuance of a CoC is not an endorsement of the research by the DHHS.

For more information about obtaining a CoC, PDs may consult with IRB staff and visit the [CoC kiosk](#) or review the [Certificate of Confidentiality Application](#) [APP03015]. For VA research, see [VHA Directive 1200.05](#).

Continuing Confidentiality Protections – Data Analysis, Dissemination and Retention

PDs should consider taking additional precautions that were not feasible while the protocol was active, including:

- Removing some or all direct identifiers (e.g., name, medical record number) and coding the information;
- Limiting the individuals who have access to the participant identifiable information;
- Employing secure archival methods or ITS-approved long-term storage services.

PDs are responsible for the secure storage of signed consent documents for at least three years after completion of the study and of HIPAA authorizations for at least six years from the date that the authorization was last in effect. PDs conducting research through Stanford University must also comply with Research Policy Handbook RPH 1.9 [Retention of and Access to Research Data](#), and should refer to this policy when considering the disposal of information.

The HIPAA privacy regulations and California law continue to apply to any PHI held for research purposes, even after the protocol has been closed.

11.3 HIPAA - Health Insurance Portability and Accountability Act Regulations

In accordance with HIPAA regulations [45 CFR 160 and 45 CFR 164], the IRB oversees the satisfaction of and compliance with some of those requirements on behalf of the portions of Stanford covered by HIPAA. This is in addition to any requirements under the Common Rule and FDA regulations. The Stanford Affiliated Covered Entity and VAPAHCS have established written policies and procedures to implement the HIPAA regulations. In accordance with the HIPAA privacy regulations, the Stanford Affiliated Covered Entity has approved and posted and the IRB adheres to a HIPAA policy specifically governing research – [1.6.2 Privacy and Security of Health Information](#). The policy describes under which circumstances protected health information (PHI) may be accessed and used or disclosed for research purposes. The following additional HIPAA policies impact investigators and the IRB:

- Stanford University [Administrative Guide Memo 1.6.2](#)
- Stanford University [HIPAA Security and Privacy policies](#)
- VAPAHCS and its physicians as health care providers also have HIPAA policies documented in [VHA Directive 1200.05](#) and [VHA Directive 6500](#), addressing research

as well as other aspects of HIPAA. VAPAHCS has a local policy (HCSM 151-15-06 - Collection, Use, Storage, and Sharing of Data in Human Subjects Research) to educate investigators and staff on these national policies.

The IRB, PDs, and other investigators accessing, using, or maintaining PHI have certain duties and responsibilities under those policies and HIPAA, particularly for research activities.

HIPAA Coordination

Stanford University has designated a University Privacy Officer who is also the privacy officer for the Stanford Affiliated Covered Entity (SACE), and a number of other privacy officials for its departments and schools. The University Privacy Officer and other privacy officials are responsible for the development and implementation of the HIPAA policies and procedures and overseeing compliance with the HIPAA Privacy Rule, as stated in [Administrative Guide Memo 1.6.2](#). The privacy officials and privacy officers meet periodically as members of the Privacy and Security Governance Council, convened by the University Privacy Officer as a forum to explore issues related to the implementation and enforcement of the Privacy and Security Rules issued under HIPAA.

VA: The VA has privacy officers at all levels: Central Office, the VISN, the Northern California Healthcare Systems, and at the Palo Alto facility (VAPAHCS). The IRB is the Privacy Board for the VA, as designated in the [Memorandum of Understanding](#).

IRB staff meet periodically with representatives of the VAPAHCS to discuss IRB matters including privacy and confidentiality issues.

11.4 Confidentiality Breach - Unauthorized Release of Information

The IRB requires that PDs immediately inform it of any possible or actual unauthorized release of information. The IRB also may receive a complaint or allegation from a participant about such a release, since its contact information is contained in the consent document for that purpose. The IRB treats such a release or allegation of release as possible non-compliance and or an unanticipated problem involving subjects or others. It follows the process set forth in [Chapter 3](#), in order to review and respond to the situation.

The IRB will report any breach of confidentiality involving VA research information to the VA Privacy Officer at the Palo Alto facility in accordance with requirements documented in the [Memorandum of Understanding](#).

California Civil Code Section 1798.80 et seq.

The response must include any notification to the participant of any breach of security relating to personal information as defined in California Civil Code Section 1798.81.5 and required by California Civil Code Section 1798.82.

Potential Violation of HIPAA

If a potential violation involves PHI, Stanford also treats it as a potential violation of HIPAA policies and the HIPAA privacy and security regulations. The IRB will communicate and coordinate its review and response with that required under the applicable Stanford HIPAA policies, including communicating with the applicable privacy officers of the Stanford organizations (refer to Stanford University [Administrative Guide Memo 1.6.2.](#))

Ch. 12: Informed Consent and Assent

The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (AAHRPP Element II.3.F)

Informed consent is a continuing process whereby the investigator and research participant have an on-going dialogue about all aspects of a research study that might inform a participant's decision to take part in the study and their decision to continue their involvement as a participant. The purpose of the consent process is to assure knowledgeable decision-making and voluntary participation.

This process generally includes:

1. Bringing the research study to the notice of potential participants;
2. Presentation and explanation of the study activities to the participant or their legally authorized representative (LAR);
3. Documentation of the informed consent via a signed and dated written consent document;
4. Ongoing discussions between the investigator and the participant regarding continued participation in the study.

The consent process must:

1. Provide sufficient opportunity for the participant, or the participant's legally authorized representative (LAR), to consider whether to participate;
2. Minimize the possibility of coercion or undue influence;
3. Be free of exculpatory language; and
4. Be in language understandable to the participant or their representative.

The IRB also requires that the circumstances of the consent process be culturally and linguistically appropriate for the intended participants.

This Chapter addresses:

- [12.1](#) Requirements for Informed Consent
- [12.2](#) Consent Procedures for Research Involving Vulnerable and Other Special Populations Including Consent by a Legally Authorized Representative
- [12.3](#) IRB Review of the Consent Process, including Consent Documents
- [12.4](#) Documentation of Informed Consent – Signature Requirements
- [12.5](#) Waiver or Alteration of Informed Consent Requirements

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[12.6](#) Exceptions to Informed Consent in Emergency Situations

[12.7](#) Observation of the Consent Process

Refer also to [Chapter 14.6](#) for more information on the consent document, and protocol director responsibilities in the informed consent process.

12.1 Requirements for Informed Consent

The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (AAHRPP Element II.3.F)

Unless waived by the IRB, legally effective informed consent must be obtained from participants or their LARs as a condition for protocol approval. All relevant requirements in OHRP in 45 CFR 46.111 and 46.116, and in the FDA regulations in 21 CFR 50.20, 50.25, 50.27 and 56.111 that are applicable to the consent process and the consent document must be satisfied.

For federally-sponsored studies, informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. See [General Requirements for Informed Consent - FDA \[GUI-C42\]](#) for FDA requirements and [General Requirements for Informed Consent-OHRP \[GUI-C41\]](#) for OHRP requirements.

Researchers are instructed to use the most recently approved consent forms, assent forms, and HIPAA Authorization forms, which are available for printing with one-click directly from the eProtocol dashboard.

IRB Evaluation of Compliance with Informed Consent Requirements

The evaluation of compliance is achieved by:

1. IRB review of the informed consent process information and document(s) provided by the PD.
2. Periodic consent form reviews comparing signed and dated consent forms with the IRB approved versions.
3. Observation of the consent process performed either as a periodic review function of the HRPP Compliance Manager, or as requested by the convened IRB. See [Chapter 12.7](#).

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12.1.1. Elements of Informed Consent

Legally effective informed consent includes the nine basic elements of informed consent and the nine additional elements of informed consent when appropriate (45 CFR 46.116, see [General Requirements for Informed Consent - OHRP \[GUI-C41\]](#)), or the eight basic elements of informed consent and the six additional elements of informed consent when appropriate (21 CFR 50.25(a),(b), see [General Requirements for Informed Consent - FDA \[GUI-C42\]](#)).

Informed consent requirements for vulnerable and other special populations are addressed in [Chapter 12.2](#).

12.1.2. Additional Consent Requirements

Stanford has and follows written policies and procedures that identify applicable laws in the localities where it conducts human research, takes them into account in the review and conduct of research, and resolves differences between federal or national law and local laws. (AAHRPP Element I.1.G)

The legal counsel to the IRB, who is a non-voting member of the IRB, can provide assistance to investigators and the IRB in resolving any conflicts among applicable laws.

1. California Law
2. VA-Specific
3. HIPAA
4. HIV Testing or Research on AIDS
5. Genetic Testing
6. Whole Genome Sequencing
7. Data and Tissue Repositories
8. Xenotransplantation
9. International research
10. Stem Cell
11. Other Federal Agencies

1. California Law

Under California Law, there are additional requirements regarding the informed consent process when certain procedures are involved.

Experimental Subject's Bill of Rights: In addition to the basic and additional elements of informed consent described above, the IRB requires that participants be given a list of their rights if participating in a “medical experiment” under California law as specified in [CA Health and Safety Code 24172](#). The California Experimental Subject’s Bill of Rights is included in the Stanford informed consent templates for medical research.

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Additional California requirements can be found in sections of this chapter that address specific consent requirements.

2. VA-Specific

For VA research, additional consent requirements might apply – refer to [VHA Directive 1200.05](#). Additional requirements include:

- i. **Payment by Veteran Participants for Treatment:** Informed consent information must include a statement that veteran-participants shall not be required to pay for treatment received as a participant in a research program. Investigators should note, however, that veterans in the "discretionary workload" category are subject to co-payments, if so, indicated by a means test. The IRB suggests that this co-payment requirement be described in the consent document. See the [VA Sample Consent template](#) for suggested language.
- ii. **Required Signatures:** The informed consent document must be signed and dated by:
 - the participant or the participant's legally authorized representative, and
 - **if required by the IRB**, a witness to the participant or the legally authorized representative's signature (not as a witness to the consent process). The witness cannot be the person obtaining consent but may be another member of the study team or may be a family member.

Note: If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person needs to serve both capacities, a note to that effect will be placed under the witness's signature line.
- iii. **A copy of the signed and dated consent document** will be given to the person signing the consent document.
- iv. **Adequate opportunity:** The investigator will give either the participant or the participant's legally authorized representative adequate opportunity to read the consent document before it is signed.
- v. The consent document must include all required **disclosures**, but does not need to use a specific template.
- vi. The IRB may **waive the requirement for the signature** of the person obtaining consent when there is no physical contact with the participant (e.g., where the only contact with the participant is through telephone or mail).
- vii. Consent may be **obtained and documented electronically** so long as there are appropriate authentication controls to provide assurance the consent is rendered by the appropriate individual, and the participant dates the consent, or software provides the current date when signed.

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- viii. When appropriate, VA requires one or more of the following elements of information be provided to each participant in addition to the basic and additional consent disclosures. Also, when any of these additional elements are appropriate, the VA requires them to be documented in the IRB-approved consent document, unless documentation of consent is waived.
 - a. If appropriate, a statement that informs VA research participants that **they or their insurance will not be charged for any costs related to the research.**
 - b. Consent for research must describe any **photographs, video, or audio recordings** obtained for research purposes; how they will be used; and whether they will be disclosed outside the VA.

3. Health Insurance Portability and Accountability Act (HIPAA)

If the protocol involves protected health information (PHI) as defined by HIPAA (refer to the Stanford University HIPAA Policy 1.6.2 [Privacy and Security of Health Information](#)), then HIPAA authorization may be included in the consent process. HIPAA authorization is an authorization to use or disclose PHI and must be executed by a separate signature.

Consent templates incorporating HIPAA authorization, and separate HIPAA authorization language are provided on the Human Subjects Research website.

4. HIV Testing; Research on AIDS

HIV counseling:

If the protocol includes testing for HIV, the consent documentation must state that identifiable participants will be informed of their results and provided with the opportunity for counseling for positive results [per California law](#).

Reportable disease testing and disclosure: ([CA Department of Public Health](#))

The [California Code of Regulations](#) requires that communicable diseases be reported to local health authorities. Individually identifiable research records generated by AIDS-related research are confidential and may only be disclosed with the prior written consent of the participant.

Any disclosure authorized by a research subject shall be accompanied by a written statement containing substantially the following language:

"This information has been disclosed to you from a confidential research record, the confidentiality of which is protected by state law and any further disclosure of it without specific prior written consent of the person to whom it pertains is prohibited."

5. Genetic Testing

If a protocol includes genetic testing, the IRB requires that the informed consent information disclose the risks specific to this type of testing. Genetic testing includes research that studies the characteristics, genes, and gene versions that are transmitted by parents to offspring. This

may include many types of information, such as personal appearance and biochemistry, gene sequences, genetic landmarks, individual or family medical histories, reactions to medication, and responses to treatment. The IRB includes detailed provisions and issues in its informed consent template that should be considered by the PD when the research includes genetic testing. The template is also used by IRB staff and members as a guide for their review of such a consent document.

6. Whole Genome Sequencing

If a protocol involving biospecimens will or may include whole genome sequencing, the IRB requires that the informed consent information disclose this to the participant. Whole genome sequencing is sequencing of a human germline or somatic specimen with the intent to generate the genome or exome sequence of that specimen.

7. Data and Tissue Repositories

The NIH [Guidance](#) on Data and Tissue Repositories is of interest to investigators who collect data or tissues of participants for repositories, and IRB staff and members who review such protocols.

When such repositories collect individually identifiable health information of participants, the HIPAA privacy regulations in [45 CFR Parts 160 and 164](#) must also be satisfied. This may require either a written HIPAA authorization from the participants or a waiver of authorization by the IRB. These requirements are discussed in [Chapter 11](#).

VA research: See [VHA Handbook 1200.12](#), Use of Data and Data Repositories in VHA Research

8. Xenotransplantation

Xenotransplantation: Any procedure that involves the transplantation, implantation, or infusion into a human recipient of either (A) live cells, tissues, or organs from a nonhuman animal source or (B) human body fluids, cells, tissues, or organs that have had ex vivo contact with live nonhuman animal cells, tissues, or organs.

In reviewing protocols and informed consent involving xenotransplantation, the IRB acts in accordance with the Guideline on Infectious Diseases Issues in Xenotransplantation issued by the federal Public Health Service (PHS) on January 19, 2001. The PHS Guidelines require that various other administrative panels (e.g., Biosafety Committee) review such protocols, in addition to the IRB. The PD should consult the PHS Guideline prior to drafting the consent document, since they contain detailed guidance about the content of the informed consent information provided to potential xenotransplantation product recipients. For example, they must be informed of the importance of complying with long-term or life-long surveillance necessitating routine physical evaluations and the archiving of tissue or body fluid specimens.

9. International Research

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When conducting research in certain communities or social contexts, whether in the U.S. or abroad, it may be inappropriate to document consent by using the standard written and signed consent document. Other consent procedures may be more culturally or socially sensitive and may afford better protection to participants. See [Chapter 1.4.1](#).

Investigators may ask the IRB to consider a waiver or alteration of some of the mandatory elements of consent [45 CFR 46.116(f)], or a waiver of documentation of consent [45 CFR 46.117(c); 21 CFR 56.109(c)]. See [Chapter 12.5](#).

Consult Legal Counsel If Necessary: PDs should contact the legal advisor to the IRBs in the Office of the General Counsel to assist in determining who under local law may serve as a legally authorized representative, if children or adults who are unable to consent may be enrolled as participants.

10. Stem Cell Research

At Stanford University, the conduct of research involving human stem cells is governed by federal, State of California, and California Institute for Regenerative Medicine (CIRM) regulations and must be reviewed by the combined IRB/SCRO (Institutional Review Board/Stem Cell Research Oversight) Panel.

See:

- Stanford University Research Policy Handbook RPH 5.8 [Human Stem Cell Research](#)
- [Stem Cell Research Oversight](#) website.

11. Requirements - Other Federal Agencies

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy, Department of Justice): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

12.1.3. Consent Templates and Glossary of Lay Terms

The [Human Subjects Website](#) provides consent form templates, including VA specific templates, which address the required elements of informed consent, as well as providing language for other situations, (e.g., related to MRI, tissue banking), in which certain additional information may need to be provided to participants. For research involving children, an [Assent Template](#) is also provided.

To assist PDs in preparing consent documents comprehensible to lay persons (i.e., at approximately 8th grade level) a glossary of lay terms is also available on the [website](#).

12.1.4. Short Form Consent Process

Federal regulations permit the use of a short form consent process (45 CFR 46.117(b)(2)) with the prior approval of the IRB when a non-English speaking participant is unexpectedly encountered. The IRB requires that a fully translated consent in the participant's language is

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provided to the participant promptly after the short form is used for certain studies involving investigational biologics, drugs, and/or devices.

The short form consent process may be approved by the IRB, on a protocol-specific basis, for use with participants who are non-English speaking. The IRB considers the study complexity and the amount and duration of participant involvement when determining if using the short form consent process is appropriate and can be approved.

For use of the short form process, the IRB determines:

- A written summary (e.g., English consent form) embodies the basic and appropriate additional elements of disclosure;
- The consent document states that the written summary has been presented orally to the participant or their legally authorized representative (LAR);
- There will be a witness to the oral presentation. The witness may be the interpreter (including the hospital interpreter), staff, a family member, or other person.
- The participant or their LAR will sign and date the consent document;
- The witness will sign and date both the short form and a copy of the summary;
- The person obtaining consent will sign and date a copy of the summary;
- A copy of the signed and dated short form will be given to the participant or their LAR; and
- A copy of the signed and dated summary will be given to the participant or their LAR.

Informed consent must begin with a concise and focused presentation of the key information that is most likely to assist a prospective subject or legally authorized representative in understanding the reasons why one might or might not want to participate in the research. This part of the informed consent must be organized and presented in a way that facilitates comprehension. Information on the requirements for use of a short form consent process is available on the RCO [website](#).

12.2 Consent Procedures for Special Populations, Including Consent by a Legally Authorized Representative

“Surrogate” and *“legally authorized representative”* have the same meaning when used in this [Chapter 12](#) and the HRPP.

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (AAHRPP Element II.4.B)

(Also addresses portions of AAHRPP Element II.4.A)

When considering approval of research, the IRB considers issues such as the selection of participants, privacy and confidentiality, coercion and undue influence, and risk-benefit analysis. Decisions are guided by the ethical principles underlying human research as set forth in the Belmont Report.

Special consideration is given to protecting the welfare of vulnerable participants, such as children, prisoners, fetuses, and mentally disabled persons, handicapped persons, or economically or educationally disadvantaged persons (45 CFR 46.111(b) and 21 CFR 56.111(b)). There are specific regulatory provisions for research involving pregnant women, fetuses, and neonates (45 CFR 46, Subpart B), prisoners (45 CFR 46, Subpart C), and children (45 CFR 46, Subpart D and 21 CFR 50 Subpart D). Special considerations for providing legally effective informed consent for these participants are discussed below:

- 12.2.1. Individuals with impaired decision-making capacity
- 12.2.3. [Children and Consenting Minors](#)
- 12.2.4. [Illiterate Participants](#)
- 12.2.5. [Non-English Speaking](#) Participants
- 12.2.6. [Prisoners](#)

Also see [Chapter 9.3](#) concerning determination of the risks to vulnerable populations as defined in applicable federal regulations, and specifically for determining the required risk categories in protocols involving children and prisoners.

Additional Requirements

Depending on the type of research project, or the source of support/funding for the study or institution at which the study will be conducted (e.g., Department of Education), other additional requirements might apply. See [Other Federal Agencies - Additional Requirements](#) [GUI-42].

12.2.1 Individuals with Impaired Decision-Making Capacity – “Decisionally impaired”

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (AAHRPP Element II.4.B)

(Also addresses portions of AAHRPP Element II.4.A)

Decisionally-impaired individuals are those with diminished capacity for judgment and reasoning due to a psychiatric, organic, developmental, or other disorder that affects cognitive or emotional functions. Other individuals may be considered decisionally-impaired or have limited decision-making ability because they are under the influence of or dependent on drugs or alcohol, suffering from degenerative diseases affecting the brain, are terminally ill, or have severely disabling physical handicaps.

The IRB must determine whether such participants should be recruited or whether support mechanisms, such as surrogate consent, are appropriate.

IRB considerations include:

- Can the person or their legally authorized representative understand the information?
- Can the person or their legally authorized representative retain enough of the information to think the question through?
- Is the person legally able to give consent?
- If not, should the person be involved in the discussion anyway?
- What are the alternatives to participation for the person? Does the person believe that those alternatives are real?
- What are the pressures on the person to consent or refuse? If surrogate permission is necessary, what are the pressures on the legally authorized representative to consent or refuse?
- Is the selection of participants equitable, particularly given the special considerations raised by research involving vulnerable populations?

Criteria for Inclusion in Research

The IRB considers and evaluates the following criteria before approving research involving adult participants with impaired decision-making capacity:

- The research must relate to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of research participants [[CA Health & Safety Code 24178\(b\)](#)]
- The research is either minimal risk, more than minimal risk with a prospect of direct benefit, or more than minimal risk without a prospect of direct benefit, but of importance to the vulnerable population
- Adequate provisions are made for obtaining consent from the participant or the participant's legally authorized representative

- Whether assent of the participants is a requirement, and, if so, whether the plan for assent is adequate
- The protocol must have an adequate plan for the assessment of the capacity to consent.

The IRB may consider additional safeguards to protect participants, such as:

- Requiring the involvement of participant advocates
- Requiring independent monitoring
- Requiring waiting periods
- Appointing a monitor to supervise the informed consent process.

Such decisions may be based on the amount of risk involved in the research and the likelihood that participants will derive health benefits from their participation.

Assessment and Determination of Incompetence

If it is believed that the prospective participant is not competent to consent for him or herself, competency must be determined by a physician (generally an investigator on the protocol). A determination of incompetence shall be made after an appropriate medical evaluation that concludes there is little or no likelihood that the participant will regain competence in a reasonable period of time, or as established by legal determination. This definition of incompetence is not limited to the legal definition but also may be a clinical judgment that a person lacks the capacity to understand the circumstances of participating in research and to make an autonomous decision to take part.

Competency should be evaluated on an individual basis to avoid incorrect assumptions as to an individual's ability to make decisions. Criteria for determining competence might vary according to the degree of risk or discomfort presented by the research procedures and the extent to which therapeutic gain can be anticipated.

Some approaches to this assessment include:

- A post-consent quiz documenting the participants' knowledge of critical elements in the informed consent document - i.e., nature of the illness being studied, voluntary nature of participation, ability to withdraw at any time, consequences of withdrawing, possible risks and benefits of participation, procedures involved, time required, confidentiality, and whom to call with any questions.
- The study investigators may ask a physician/psychologist outside the research team to evaluate the potential participant's decisional capacity.

The IRB may consider additional safeguards to protect participants, such as:

- Requiring the involvement of participant advocates
- Requiring independent monitoring
- Requiring waiting periods

- Appointing a monitor to supervise the informed consent process.

Such decisions may be based on the amount of risk involved in the research and the likelihood that participants will derive health benefits from their participation.

Obtaining Consent from a Legally Authorized Representative

The IRB, consistent with state and federal human subjects regulations, requires that consent for research be obtained from the participant's legally authorized representative, if the subject lacks the capacity to consent (e.g., OHRP 45 CFR 46.116, FDA 21 CFR 50.20, CA Health & Safety Code 24178). [Section 24178 of the California Health and Safety Code](#) specifies the legally authorized representative of the participant in most (but not all) research situations for California and its requirements must be met before a surrogate may be used under its provisions.

See guidance [Research Surrogate Decision-Makers - Section 24178 of the California Health and Safety Code](#) [GUI-32].

Participants in Psychiatric Units or Mental Health Facilities: Special Rules

Surrogates for an inpatient on a psychiatric unit or in a mental health facility or a patient on a psychiatric hold may not be able to consent for research under different state laws, particularly if the research participant has been adjudicated to lack the capacity to consent and a conservator appointed. An investigator who proposes to involve such participants with the possible need for surrogate decision makers should discuss the situation with the IRB staff or the IRB legal advisor in the Office of the General Counsel.

12.2.2 Pregnant Women, Fetuses and Neonates

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (AAHRPP Element II.4.B)

In accordance with OHRP, the IRB requires that additional protections be provided to pregnant women, fetuses and neonates involved in research. General considerations related to research involving pregnant women, fetuses and neonates are set out in [Chapter 9](#). The special informed consent requirements are specified in 45 CFR 46, Subpart B (OHRP) and are summarized in the guidance [Research Involving Pregnant Women, Fetuses, and Neonates](#) [GUI-8].

Pregnant Children

If the pregnant person is under the age of 18 and is not emancipated, the IRB generally requires, consistent with OHRP, that parental permission and child assent be obtained. If the research is therapeutic, and the PD believes that the child's participation in the research falls

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into one of the categories under California law where an unemancipated minor is permitted to consent to her own medical care, the PD should confirm this with IRB staff or the IRB legal advisor in the Office of the General Counsel.

Nonviable Neonates

Consent may not be obtained from a legally authorized representative of either or both of the parents of a nonviable neonate. The IRB will not permit elements of the informed consent process to be altered or waived in research involving nonviable neonates, even if the general requirements for waiver are satisfied.

When it has been determined that the neonate is viable, the neonate is considered a child and the consent requirements laid out below apply.

12.2.3 Children and Consenting Minors

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (AAHRPP Element II.4.B)

The IRB imposes additional protections on research involving children, in accordance with 45 CFR 46, Subpart D and 21 CFR 50, Subpart D.

By regulatory definition, “children” are persons who have not attained the legal age for consent to treatments or procedures involved in the research, under the applicable law of the jurisdiction in which the research will be conducted. In California, a person under 18 years old is considered a “child,” and may not legally give consent, although there are certain exceptions for emancipated and self-sufficient minors.

Since children cannot legally give consent, informed consent must be obtained from parents (“parental permission”), or the legally appointed guardian. The IRB requires the investigator to obtain the permission of a child's parent(s) or guardian before enrolling the child in a study. See guidance [Parental Permission](#) [GUI-C34].

Assent

When, in the judgment of the IRB, the children are capable of providing assent the IRB may determine that assent is required, that adequate provisions are made for soliciting the assent of the children, and whether and how assent must be documented. Generally, children aged 7 and above may be asked to give their assent to participation.

When Minors, Including Emancipated Minors, may Consent as Adults

In accordance with California law, there are certain situations in which the IRBs permit minors to consent to participation in research as adults without parental permission. If the protocol director is not familiar with such laws, he or she may need to consult with IRB staff or the IRB legal advisor in the Office of the General Counsel prior to enrolling a minor in a research study

without parental permission, to ensure that the applicable legal requirements are met. The criteria under which a waiver of parental permission may be granted are discussed in the guidance [Consent for Protocols Involving Children and Consenting Minors](#) [GUI-C24].

See guidances:

- [Consent for Protocols Involving Children and Consenting Minors](#) [GUI-C24]
- [Parental Permission](#) [GUI-C34]
- [Chapter 12.4](#) for information on documentation of informed consent, and assent.

12.2.4 Illiterate Participants

The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (AAHRPP Element II.3.F)

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (AAHRPP Element II.4.B)

The IRB allows individuals who speak and understand English, but who cannot read the consent materials due to illiteracy, to enroll in a study by “making their mark” (e.g., signing or marking an “X”) on the consent document, after going through the informed consent process. This also applies to individuals who speak a language that does not have a written form.

If a participant, or their LAR, is illiterate:

- Information in the consent materials should be presented orally, including the California Experimental Subject’s Bill of Rights (as appropriate, and for clinical investigations)
- Sufficient time should be allowed for questions to be asked and answered, both by the participant, and by the person obtaining consent to ensure the participant comprehends the consent information.

Additionally, FDA guidance on [Illiterate English Speaking Subjects](#) contains recommendations for documenting the consent process when a participant is competent and understands and comprehends spoken English, but is physically unable to talk or write, but can indicate approval or disapproval by other means:

- An impartial witness, present during the entire informed consent discussion, signs and dates the consent document,
- Videotaping the consent discussion might be considered,
- The person obtaining consent (POC) might document on the consent form the method used for communication with the prospective subject and the specific means by which the prospective subject communicated agreement to participate.

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Participants (or their LARs) must be given a copy of the signed consent document(s), and any other written information provided to participants.

12.2.5 Non-English Speaking Participants

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (AAHRPP Element II.4.B)

Stanford University is located in a culturally diverse region of California. Investigators are encouraged to recruit and include all segments of the community in research, including individuals whose primary language is not English.

Participants who are not fluent in English should be presented with a consent document written in a language understandable to them that embodies all the elements necessary for legally effective informed consent.

The Stanford HRPP and Office for Human Research Protections encourages the use of a full consent form translated into the participant's language whenever possible. When all of the participants in a study (i.e., the target population) are anticipated to be non-English speaking, a full translated consent is required and needs IRB approval before use. Refer to the [Human Subjects Website](#) for information on translating consent forms. If a non-English speaking participant is unexpectedly encountered and initially consented through an approved short form process and the study involves certain investigational biologics, drugs, and/or devices the IRB requires that a fully translated consent form in the participant's language be promptly provided to the participant.

When a full-length form embodying all elements of consent is required by the IRB to document consent, the IRB requires that appropriately translated consent documents be submitted to the IRB for review and approval prior to their use in enrolling participants.

Investigators may use language translators or interpreter services to obtain consent in a language understandable to the participant or the participant's legally authorized representative. The person obtaining consent may not serve as the witness. The IRB may utilize expedited review procedures in approving such documents if the English language consent document has already been approved.

Short Form Consent Process

Federal regulations permit the use of a short form consent process (45 CFR 46.117(b)(2) and 21 CFR 50.27(b)(2)) with the prior approval of the IRB; for more information see [Chapter 12.1.4](#) above, and the [Human Subjects Website](#).

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12.2.6 Prisoners

The IRB has and follows written policies and procedures requiring appropriate protections for prospective participants who cannot give consent or whose decision-making capacity is in question. (AAHRPP Element II.4.B)

The IRB considers prisoners to be a vulnerable population because both their incarceration and the constraints imposed on them during their incarceration may render them unable to make a truly informed and voluntary decision regarding whether to participate in research. The IRB imposes additional protections pertaining to biomedical and behavioral research involving prisoners, limits the types of research that can be approved, and requires special consent information as specified in OHRP in 45 CFR 46 (Subpart C) and Sections 3521-3522 of the California Penal Code. [Involvement of Prisoners in Research](#) [GUI3010] is provided. (See [Chapter 9](#) for an explanation of these additional safeguards.) If the Protocol Director (PD) is not familiar with these legal requirements, the PD who proposes to involve prisoners in research should contact IRB staff or the IRB legal adviser in the Office of General Counsel prior to submission of the protocol and consent document to the IRB for review.

As required by California law regarding prisoner research, the IRB evaluates the consent process and the consent document to ensure that the information disclosed to the participant covers the requirements of [California Penal Code Sections 3521-3522](#). These California consent requirements duplicate requirements already covered by OHRP, except for the requirement that the prisoner participant be informed of the expected recovery time after completion of the experiment.

Prisoners at VA Facilities

The IRB, consistent with VA policy, prohibits research on prisoners conducted by VA investigators while on official duty, or at VA facilities unless a waiver has been granted by the Chief Research and Development Officer. ([VHA Directive 1200.05](#)). If the waiver is granted, the research must be conducted in accordance with the general IRB policies and procedures specified above.

12.3 IRB Review of the Consent Process, including Consent Documents

The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (AAHRPP Element II.3.F)

PDs should refer to [Chapter 14.6](#) for information regarding the development of an informed consent process and method of documentation appropriate to the type of research and the study population.

PDs must submit for IRB review any consent document(s) and explanation of the circumstances under which informed consent will be sought for new protocols, at continuing review, and whenever a modification to the consent process or documents is requested.

The [Protocol Application](#) (forms [on Forms and Templates page](#)) solicits the information necessary for the IRB to evaluate whether the informed consent process will be appropriately conducted given the protocol-specific circumstances (e.g., level of risk, inclusion of special participant populations) and adequately protects participants, considering issues such as whether:

1. Participants have sufficient time to discuss concerns and decide whether to participate in the research;
2. The possibility of coercion and undue influence is minimized;
3. Communications to the participant or their LAR are in a language understandable to them; and
4. Consent process communications do not include any exculpatory language through which the participant or their LAR is made to waive, or appear to waive, any of the participant's legal rights, or which releases or appears to release the investigator, sponsor, institution, or agents from liability for negligence.

The same evaluation criteria apply to review and approval of the consent process and consent document(s) when reviewed by the expedited process, as by regular review.

The IRB staff review the consent document(s) and consent process information (see [Informed Consent Checklist on Forms and Templates page](#).) For continuing review or modifications, any new information that could impact participants' risks (e.g., adverse events) or procedure changes are also examined to ensure the consent document is appropriately updated. Re-consent may be required. Examples of when re-consent might be required include when there is new information (e.g., risks, procedures, etc.) that could impact participants' willingness to participate, or any other time the IRB determines it is necessary. Consent process requirements are discussed in [Chapter 12.1](#) above.

The IRB considers the relationship between the person(s) who will solicit, obtain consent, and explain the consent document and the potential participant. The IRB requires that the circumstances of the consent process be culturally and linguistically appropriate for the intended participants and protects participants by minimizing the possibility of coercion and undue influence and allowing adequate time for them to discuss and decide whether to participate in the research.

The IRB also reviews any direct advertising (e.g., newspaper, TV or radio ads, posters, flyers, letters or postcards, emails, postings on bulletin boards/ internet/ web), since it is considered by the FDA "to be the start of the informed consent and subject selection process." In order to approve advertisements, the IRB must determine that the direct advertising is not unduly coercive and does not promise a certainty of cure or favorable outcome or other benefits

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beyond what is outlined in the consent and the protocol. (See [Chapter 10.](#)) See guidance [Advertisements: Appropriate Language for Recruitment Material](#) [GUI-16].

Consideration at an IRB Convened Meeting

The IRB determines that all basic, and all additional elements appropriate to the research, are included in the consent process. All the relevant requirements in OHRP in 45 CFR 46.109(b) and 46.116, and in the FDA regulations in 21 CFR 56.109(b), 50.20 and 50.25, that are applicable to the consent process and the consent document, must be satisfied for IRB approval.

The IRB may require revisions to the consent document as a condition for approval. If the revisions are minor and can be dictated verbatim at the meeting, the protocol may be approved contingent upon the revisions being made. The IRB will determine if a member or IRB staff can confirm that the revisions have been implemented as specified before the contingency can be removed. If revisions are greater than minor or cannot be dictated verbatim at the convened meeting, the protocol is tabled, and the consent document is referred back to the PD for the drafting of the revisions and submission at a future convened meeting. If the PD disagrees with the verbatim revisions specified by the IRB, the protocol is tabled, and the PD must submit a revised consent document for future consideration.

The approval date and the expiration date must be added to the consent document(s). (See [Chapter 14.6](#)).

Additional Requirements

See [Other Federal Agencies - Additional Requirements](#) [GUI-42].

12.4 Documentation of Informed Consent – Signature Requirements

The IRB has and follows written policies and procedures to evaluate the consent process and to require that the Researcher appropriately document the consent process. (AAHRPP Element II.3.F)

Documentation of informed consent refers to a participant, or their legally authorized representative (LAR), signing and dating an IRB-approved, dated consent document, which includes the nine basic elements of informed consent and the nine additional elements of informed consent when appropriate (45 CFR 46.116, see [General Requirements for Informed Consent - OHRP](#) [GUI-C41]), or the eight basic elements of informed consent and the six additional elements of informed consent when appropriate (21 CFR 50.25(a),(b), see [General Requirements for Informed Consent - FDA](#) [GUI-C42] (;).

When a person agrees to be a participant in a research study, signing the consent document indicates that they have participated in the consent process, and understand the information provided to them.

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Documentation requirements for informed consent are specified in OHRP in 45 CFR 46.117(a),(b) and FDA 21 CFR 50.27(a),(b).

In order to approve research, the IRB must determine that informed consent will be appropriately documented, unless the IRB waives documentation under OHRP or FDA regulations (see [Chapter 12.5.2](#)). If a participant lacks the capacity to consent, then consent for research must be obtained from their LAR. See [Chapter 12.2](#) above, and [Research Surrogate Decision-Makers - Section 24178 of the California Health and Safety Code](#) [GUI-32].

Consent is documented through use of a written consent document signed and dated by the participant or their legally authorized representative that embodies all of the required elements of informed consent (see [Chapter 12.1](#)). Only the IRB-approved informed consent document may be used, and unless the requirement is waived by the IRB, the document must be signed by the participant (or the participant's LAR), and a copy must be given to the person signing the form. FDA regulations require that the signature be dated.

Stanford Hospital and Clinics (SHC), the Lucile Packard Children's Hospital (LPCH) and Stanford University policies stipulate that the signed consent document must be scanned into the participant's medical record. The VA has a similar requirement.

Short Form Consent Process – Additional Signature Requirements

Subject to prior approval of the IRB, consent may be documented through use of a short form written consent document with the requirements and process specified in OHRP 45 CFR 46.117(b)(2) and the FDA regulations in 21 CFR 50.27(b)(2). The short form consent process is generally applicable to situations involving non-English participants. If the participant agrees to take part in the study, the following signatures are required:

On the short form consent document (translated):

- i. Participant or the participant's [legally authorized representative \[LAR\]](#)
- ii. Witness (the interpreter may act as the witness)

On the summary form (English):

- i. Person obtaining consent
- ii. Witness (the interpreter may act as the witness)

For information on using the short form consent process see [Chapter 12.1.4](#) above and the [Human Subjects Website](#).

Children Participants, Documentation of Informed Consent, and Assent

Since children cannot legally give consent, informed consent must be obtained from parents ("parental permission"), or the legally appointed guardian. For information on the requirements for documentation of consent for children participants, see [Consent for Protocols Involving Children and Consenting Minors](#) [GUI-C24] and [Parental Permission](#) [GUI-C34].

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When, in the judgment of the IRB, the children are capable of providing assent, the IRB may determine whether and how assent must be documented. See the [Assent Template](#) and [Chapter 12.2.3](#).

12.5 Waiver or Alteration of Informed Consent Requirements

The IRB has and follows written policies and procedures for approving waivers or alterations of the consent process and waivers of consent documentation. (AAHRPP Element II.3.G)

- Waiver or alteration of the consent process
- Waiver of documentation of informed consent – (“waiver of signature”)

12.5.1 Waiver or Alteration of the Consent Process

Under OHRP 45 CFR 46.116(e) (f), and (g), IRBs have authority to alter or waive the requirement to obtain informed consent. FDA [21 CFR 50.22](#) also allows for this process for certain FDA-regulated minimal risk clinical investigations. FDA does not allow for waivers of parental permission for studies that fall under 45 CFR 46.408(c).

FDA regulations provide for exceptions to the informed consent requirements for emergency use of a test article (see [Chapter 5.8](#)), and waivers granted for planned emergency research (see [Chapter 12.6](#)).

The IRB may approve an investigator’s request to waive or alter the requirement to obtain informed consent if the investigator demonstrates with specificity that the waiver or alteration criteria are met. To approve such a request, the IRB must find and document the following:

1. The research or clinical investigation involves no more than minimal risk to the subjects;
2. The research or clinical investigation could not practicably be carried out without the waiver or alteration;
3. If the research involves using identifiable private information or biospecimens, the research could not practicably be carried out without using such information or biospecimens in an identifiable format;
4. The waiver or alteration will not adversely affect the rights and welfare of the subjects; and
5. Whenever appropriate, subjects or LARs will be provided with additional pertinent information after participation.

Under 45 CFR 46.116(e) the IRB may waive or alter the consent process when:

1. The research or a demonstration project is to be conducted by or subject to the approval of state or local government officials and is designed to study, evaluate, or otherwise examine:

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- (i) public benefit or service programs;
- (ii) procedures for obtaining benefits or services under those programs;
- (iii) possible changes in or alternatives to those programs or procedures; or
- (iv) possible changes in methods or levels of payment for benefits or services under those programs; and

2. The research could not practicably be carried out without the waiver or alteration.

To request a waiver or alteration of the informed consent process the investigator must demonstrate that each of the criteria under Section 45 CFR 46.116 (e) or (f) (OHRP) or per FDA guidance is met for the given protocol. (See [Protocol Application](#)).

To approve a waiver or alteration of the informed consent process the IRB must find and document that all regulatory criteria under 45 CFR 46.116 (e) or (f) (OHRP) or per FDA guidance are met.

Special Considerations for Research Involving Deception

In research involving deception, the investigator may, with protocol-specific justification, request an alteration of the consent process. The IRB may approve the research, including the request to alter the requirement for informed consent if the investigator demonstrates that deception or incomplete disclosure is necessary and addresses concerns relating to participant protection; e.g., debriefing.

Screening, Recruiting, or Determining Eligibility

The IRB may approve a research proposal in which an investigator will obtain information or biospecimens for the purpose of screening, recruiting, or determining the eligibility of prospective subjects without the informed consent of the prospective subject or the subject's legally authorized representative, if either of the following conditions are met:

- (1) The investigator will obtain information through oral or written communication with the prospective subject or legally authorized representative, or
- (2) The investigator will obtain identifiable private information or identifiable biospecimens by accessing records or stored identifiable biospecimens.

Research Involving Children: Waiver of Parental Permission/Guardian Consent

The IRB will often consider a request for a waiver or partial waiver of parental permission for minimal risk research to be conducted in a classroom.

The IRB may waive parental permission by determining that the criteria for waivers or alterations are met. However, research is ordinarily not suitable for a waiver of parental permission if it involves any of the following issues:

- 1. Parental political affiliations or beliefs

2. Mental or psychological problems
3. Sexual behavior or attitudes
4. Illegal, antisocial, or self-incriminating behavior
5. Appraisals of other individuals with whom the minor has a familial relationship
6. Relationships legally recognized as privileged (lawyers, doctors, clergy), and
7. Religious affiliations or beliefs.

If the IRB waives the requirement for parental permission, it may require an alternative mechanism to protect the child participants (e.g., appoint a qualified child advocate).

Additional Requirements - Other Federal Agencies

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy, and Department of Education (such as compliance with Family Educational Rights and Privacy Act (FERPA)): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

12.5.2 Waiver of Documentation of Consent – (“waiver of signature”)

As allowed by OHRP (45 CFR 46.117 (c)) ,FDA regulations (21 CFR 56.109(c)) and the VA ([VHA Directive 1200.05](#)), the IRB may waive the requirement to obtain written documentation of informed consent. This provision can be used only for the waiver of documentation of consent, not for waiver or alteration of the consent process itself. A waiver of documentation of consent does not mean that requirements of the consent process are removed.

Even if a waiver of documentation is granted by the IRB, permitting the investigator to forego obtaining the participant’s signature on a written consent document, the investigator still must provide the participant with all of the information described in [Chapter 12.1](#) required to constitute a complete and appropriate consent process, through an information sheet, or through an oral script in a language understandable to the participants. In all cases in which the requirement for documentation of consent is waived, the IRB may require the PD to provide participants with the written consent document with an option to sign the consent document, or with a written statement regarding the research.

To approve a waiver of documentation, the IRB must find that the protocol-specific justification for waiving documentation satisfies regulatory criteria. Specifically, the IRB must determine the regulatory basis for the waiver as one of the following (***note that a) does not apply for FDA-regulated research***):

- (a) Under OHRP (45 CFR 46.117(c)(1)) the IRB must find and document either:
 - i. the only record linking the participants and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality. Each participant will be asked whether he/she wants documentation linking the participant with the research, and the participant’s wishes will govern; or

- ii. the research presents no more than minimal risk of harm to participants and involves no procedures for which written consent is normally required outside of the research context; or
- iii. if the subjects or legally authorized representatives are members of a distinct cultural group or community in which signing forms is not the norm, that the research presents no more than minimal risk of harm to subjects and provided there is an appropriate alternative mechanism for documenting that informed consent was obtained;

OR

- (b) For research subject to OHRP **and FDA** regulations, the IRB must find and document that the research involves no more than minimal risk to participants and involves no procedures for which written consent is normally required outside of the research context. (45 CFR 46.117(c)(1)(ii), 21 CFR 56.109(c)(1)).

Guidance [Findings for Waiver or Alteration of Consent Requirements and Findings for Waiver of Documentation \(Including Signature\) of Consent](#) [GUI-C2] is available to IRB members and on the Human Subjects Research website.

Waiver or Alteration of HIPAA Authorization

In order to waive or alter an authorization, the investigator must provide sufficient information on which the IRB may make the following three findings specified by the Privacy Rule (45 CFR 164.512(i)(2)(ii):

- A. The use or disclosure of protected health information (PHI) involves no more than minimal risk to the privacy of individuals based on;
 - 1. An adequate plan to protect the identifiers from improper use and disclosure;
 - 2. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research, unless there is a health or research justification for retaining the identifiers, or such retention is otherwise required by law; and
 - 3. Adequate written assurances that the protected health information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research project, or for other research for which the use or disclosure of protected health information would be permitted by the Privacy Rule;
- B. The research could not be practically conducted without the waiver or alteration; and
- C. The research could not be practically conducted without access to and use of the protected health information.

See Stanford University HIPAA Policy 1.6.2 [Privacy and Security of Health Information](#).

12.6 Exceptions to Informed Consent in Emergency Situations

The IRB has and follows written policies and procedures for making exceptions to consent requirements for planned emergency research and reviews such exceptions according to applicable laws, regulations, codes, and guidance. (AAHRPP Element II.4.C)

Note: “Planned emergency research” **is not synonymous with** “emergency use of a test article”, which is addressed in [Chapter 5.8](#).

Planned emergency research refers to research planned for emergency settings, including the planned use of a test article.

Planned emergency research involves an extensive approval process, including FDA approval, prospective IRB review, and approval and consultation with representatives of the communities where the research will be conducted and from where participants will be drawn. Investigators must submit a protocol application including a description of the informed consent process or a request to waive informed consent; often in emergency settings it is not possible to obtain informed consent from a potential participant when there is insufficient time and a legally authorized representative (LAR) is not available.

The IRB may waive the requirement for informed consent in accordance with an exception under 21 CFR 50.24 (FDA) or 45 CFR 46.101(i) or 45 CFR 46.116(j) (OHRP), depending on whether or not the research is subject to FDA regulation, given that all required IRB determinations under these provisions can be made. Under these regulations, the IRB may permit planned research in an emergency setting without the informed consent of the participants or their legally authorized representatives in a limited class of emergent situations where the participant is in need of an emergency experimental intervention but cannot give informed consent due to a life-threatening medical condition and there is not sufficient time to obtain consent from the participant’s legally authorized representative. (This does not apply to VA research – see below.)

In addition, advance notice of such planned emergency research protocols will be provided to the Office for Human Research Protections pursuant to 45 CFR 46.101(i).

See also:

- [Informed Consent Requirements in Emergency Research](#) [OHRP]
- [Exception from Informed Consent for Studies Conducted in Emergency Settings](#) [FDA]

VA Research

Planned emergency research cannot be conducted by the VA. See [VHA Directive 1200.05](#).

Additional Requirements - Other Federal Agencies

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Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy (such as who may grant waivers of the consent process and human research protections policy requirements): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

12.7 Observation of the Consent Process

Stanford has and follows written policies and procedures that allow the Institutional Review Board to function independently of other organizational entities in protecting research participants. (AAHRPP Element I.1.C)

See the Charges by the Vice Provost and Dean of Research to:

- The [Administrative Panel on Human Subjects in Medical Research – IRB](#)
- The [Administrative Panel on Human Subjects in Medical Research – IRB/SCRO](#)
- The [Administrative Panel on Human Subjects in Nonmedical Research](#).

As part of the IRB oversight options, the IRB may require that a staff member or an outside third party observe the consenting of research participants to determine:

- Whether the informed consent process has been appropriately completed and documented;
- Whether the participant has had sufficient time to consider study participation, that no coercion has been used by the consenting staff; and
- That the information presented to the participant reflects the content of the consent form and is conveyed in understandable language.

The IRB may require that one or more informed consent process situations be observed for selected protocols. IRB considerations used to choose such protocols include:

- High risk studies
- Studies that involve particularly complicated procedures or interventions
- Studies involving potentially vulnerable populations (e.g., ICU patients, children)
- Studies involving study staff with minimal experience in administering consent to potential study participants, or
- Situations when the IRB has concerns that the consent process is not proceeding well.

See:

- [Consent Observation Checklist](#) [CHK-C15].

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12.8 Broad Consent

Broad consent for the storage, maintenance, and secondary research use of identifiable private information or identifiable biospecimens (collected for either research studies other than the proposed research or non-research purposes) is permitted by [45 CFR 46.116\(d\)](#) as an alternative to the informed consent requirements. Stanford is not utilizing this process currently.

Ch. 13: Communication among IRBs in Cooperative (Multi-Site) Research

13.1 Communication among IRBs in Cooperative (Multi-Site) Research

Stanford ensures that the Human Research Protection Program has resources sufficient to protect the rights and welfare of research participants for the research activities that Stanford conducts or oversees. (AAHRPP Standard I-2)

The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization, the rights and welfare of research participants are protected. (AAHRPP Element I.9)

The IRB is responsible for the review of all Stanford research that involves human research participants, whether the research is conducted at Stanford University, a Stanford affiliate institution, or another site outside [Stanford](#).

When Stanford is conducting research at an external site (e.g., nursing home, school) and is not the coordinating site or lead investigator, and that site is engaged in research, the IRB requires contact information for the coordinating/lead site, whether the site has an IRB, and confirmation of the IRB’s permission to conduct the research.

Stanford relies on the IRBs of other sites, and agrees to have other sites rely on Stanford’s IRB when mandated. When the Single IRB (sIRB) process is used, an agreement is signed by the institutional officials of Stanford and the other site(s). Stanford uses the SMART IRB reliance, which supports IRB reliance across the nation. SMART IRB provides assurance of an evaluation process, delineates responsibilities, and documents reliance agreements. The sIRB manager(s) process authorization agreements, conduct local context reviews, and answer reliance questions. Stanford University also participates in the independent model of the Adult and Pediatric Central Institutional Review Board (CIRB) Initiative of the National Cancer Institute (NCI). The CIRBs are the IRB of record for certain adult and pediatric national multi-center cooperative oncology group cancer treatment trials.

Mandated Single IRB (sIRB)

45 CFR 46.114 states that (a) Cooperative research projects are HHS non-exempt (or exempt research for which limited IRB review takes place pursuant to 45 CFR 46.104(d)) projects that involve more than one institution. In the conduct of cooperative research projects, each institution is responsible for safeguarding the rights and welfare of human subjects and for complying with this policy.

(b)(1) Any institution located in the United States that is engaged in cooperative research must rely upon approval by a single IRB for that portion of the research that is conducted in the United States. The reviewing IRB will be identified by the Federal department or agency

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supporting or conducting the research or proposed by the lead institution subject to the acceptance of the Federal department or agency supporting the research.

(b)(2) The following research is not subject to this provision: (i) Cooperative research for which more than single IRB review is required by law (including tribal law passed by the official governing body of an American Indian or Alaska Native tribe); or (ii) Research for which any Federal department or agency supporting or conducting the research determines and documents that the use of a single IRB is not appropriate for the particular context.

(c) For research not subject to paragraph (b) of this section, an institution participating in a cooperative project may enter into a joint review arrangement, rely on the review of another IRB, or make similar arrangements for avoiding duplication of effort.

Stanford Serving as Reviewing IRB

If a federal grant mandates a single IRB for cooperative research, Stanford facilitates with investigators to utilize one of the following: commercial IRB, TIN network IRBs other academic IRB, or Stanford IRB (e.g., in the case of Small Business Innovation Research).

Relying on a Single IRB (sIRB)

Stanford may agree to rely on a single IRB (sIRB) for multisite and cooperative studies to provide initial and ongoing regulatory reviews. The reliance terms are outlined in the SMART IRB authorization agreement. The sIRB is responsible for reviews required by federal regulations at 45 CFR 46, and 21 CFR 50 and 56 (initial review, continuing review, modifications, reportable events). When Stanford IRB relies on a sIRB, Stanford still retains responsibility to ensure investigator compliance with the protocol, the sIRB's determinations, applicable federal and state regulations, and Stanford policy. Stanford bears responsibility for the local context (e.g., local ancillary requirements, managing reliance agreements, and handling study specific issues that arise).

The Protocol Director (PD) is required to submit a [sIRB eProtocol application](#) to request reliance on a sIRB and receive acknowledgement from RCO and approval from the reviewing IRB before beginning research.

Stanford Serving as Participating Institution

When Stanford is a participating institution (e.g., sending data or tissue samples out of Stanford, etc.) the PD must submit data in a timely manner to the coordinating institution, report unanticipated problems (UPs) and other reportable events in a timely manner to the coordinating institution and the Stanford University IRB, and ensure that the PD's study team has the current approved version of the protocol and consent form.

The IRB Role in the NCI Central IRB (CIRB) Initiative

The NCI CIRB Initiative is sponsored by the National Cancer Institute in consultation with the Department of Health and Human Services Office for Human Research Protections (OHRP). Stanford University via IRB staff function as a liaison between the CIRB and the investigators, and as a resource to investigators when needed.

Stanford participates in the independent CIRB model. The IRB staff complete the Annual Institutional Worksheet which apprises the CIRBs of local context, includes required informed consent template language, applicable local and State regulations, and Stanford policies. Investigators submit an Annual Investigator Worksheet for each investigator, and a Study-specific Worksheet for each study in which they wish to enroll participants directly to the CIRB. The CIRB is responsible for initial and continuing review, review of subsequent modifications, non-compliance, and unanticipated problems. CIRB copies the IRB on notices when studies are initiated or closed. Stanford receives notification from CIRB of local serious or continuing noncompliance and unanticipated problems.

VA protocols are not involved in this initiative.

13.2 Information Management in Cooperative (Multi-Site) Research

<i>The organization has written policies and procedures to ensure that, when sharing oversight of research with another organization, the rights and welfare of research participants are protected. (AAHRPP Element I.9)</i>
<i>The IRB has and follows policies and procedures for managing multisite research by defining the responsibilities of participating sites that are relevant to the protection of research participants, such as reporting of unanticipated problems or interim results. (AAHRPP Element II.2.I)</i>

Stanford Serving as Coordinating Institution

When Stanford is serving as the coordinating institution, the PD must describe the plans for communicating information relevant to the protection of participants among the participating sites and institutions as part of the Protocol Application, including communications of adverse outcomes, UPs, protocol modifications, and interim results. When the Stanford PD is the lead researcher, the IRB evaluates whether the management of information that is relevant to the protection of participants is adequate.

When completing the Protocol Application, PDs must indicate if Stanford is serving as the coordinating institution. The PD must list all other sites involved with the proposed research, the contact person at each site and contact information, such as phone number and email address. The PD must indicate if each participating site has an IRB and if that IRB has reviewed and approved the research.

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When Stanford is the coordinating institution receiving data or tissue samples from other sites, the PD must submit the following documentation for each of the other participating sites along with the Protocol Application to the IRB before receiving any data or tissue samples from a site:

- IRB approval letter from each participating site that includes the type of review, the other institution's FWA information, and
- When appropriate, the consent forms from all participating sites.

The Stanford University IRB will keep this information on file for all internal and external reviews.

By submitting the protocol application form, the PD documents their acceptance of the responsibility of ensuring that all participating sites have obtained IRB approval prior to initiation of the research at that site. The participating sites must have written procedures that define the scope of studies subject to review by their IRB. The Stanford University IRB staff will review and confirm that each protocol application for a Stanford coordinating site project includes the appropriate documentation from all participating institutions.

For a prospective clinical trial, the consent forms used at all sites must indicate that data or samples are being sent to Stanford. Data or tissue samples, even if they are anonymous, may not be received from an outside institution whose consent form prohibits data or tissue from being sent outside the institution.

There must be documentation of regular communication (e.g., teleconferences) with the participating sites to update and inform all participating sites about progress of the study.

Reporting to the IRBs in Cooperative (Multi-Site) Research

As the lead investigator at the coordinating institution, the PD is responsible for receiving data and reports from the outside sites in a timely manner and distributing them to the Stanford University IRB as required - see [Chapter 3.10](#). Stanford IRBs give the same considerations to such reports in cooperative (multi-site) research as they do to internal reports.

Identifying Material Changes in Cooperative (Multi-Site) Protocols

The PD must report any material changes in the protocol that take place at any of the participating research sites. The IRB may require independent verification to ensure that no material changes have occurred in multi-site or cooperative research since the previous IRB review.

Additional Requirements

VA Cooperative (Multi-Site) Research: When engaged in collaborative research with VAPAHCS, each institution must use the informed consent document required by its respective institutional policies for participants recruited from that institution, or procedures requiring participation of the subject at that institution. The informed consent document may contain

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information on the project as a whole as long as the document clearly describes which procedures will be performed under VA’s auspices and which will be performed under a non-VA institution’s auspice.

The VA informed consent document must clearly state when procedures conducted at other non-VA institutions are part of the VA’s portion of the study.

The informed consent document and HIPAA authorization (for the VA portion of the collaborative study) must not contain inconsistent provisions. Refer to [VHA Directive 1200.05](#) for local approvals required.

Other Federal Agencies: Additional requirements might apply, (such as a formal agreement to specify the roles and responsibilities of each party), depending on the source of support/funding (e.g., Department of Defense, Department of the Navy). See [Other Federal Agencies - Additional Requirements](#) [GUI-42].

Ch. 14: Protocol Director Standards

Stanford policies, procedures, and education programs help Protocol Directors (PDs) and all Stanford investigators carry out research studies in an ethical manner. In addition to following applicable federal, state, and local regulations, investigators follow ethical principles outlined in the Belmont Report and standards appropriate for their discipline. In designing and conducting clinical trials, PDs follow Good Clinical Practice (GCP) guidelines defined by the Food and Drug Administration and have the protection of participants' rights and welfare as their primary concern.

14.1 Identification and Management of Conflict of Interest

Researchers and Research Staff identify and disclose financial interests according to organizational policies and regulatory requirements and, with Stanford, manage, minimize, or eliminate financial conflicts of interest. (AAHRPP Element III.1.B)

PDs and research staff are expected to follow Stanford University policies addressing the disclosure of conflicts of interest as described in [Chapter 3.7](#) and the policies referenced therein.

Disclosures of potential conflicts of interest are reviewed and resolved by the COIRP/COIC. The IRB has the final authority to decide whether the potential conflict of interest and its management, if any, allows the research to be approved.

See [Chapter 3.7](#) and [Chapter 6.3](#).

14.2 Sound Study Design

Researchers employ sound study design in accordance with the standards of the discipline. (AAHRPP Element III.1.C)

The significance of the research depends upon the validity of the results. It is unethical to put subjects at risk or to inconvenience them through participation in a study that may produce little or no reliable information. Regardless of the source of funding, it is the PD's responsibility to judge the research design to be sound enough to meet its objectives before submitting the protocol for IRB review. The Protocol Application provides questions addressing the various considerations for sound study design. When designing studies, the PD should consult [Evaluating Sound Study Design](#) [GUI-17] and include all pertinent information in the Protocol Application. The Protocol Application also includes a description of the provisions for monitoring the data and reporting to the IRB and other entities (see [Chapter 14.3](#) below).

In developing, or in evaluating the adequacy of, a research design involving investigational drugs or biological products, the PD should refer to the FDA [Guidance Documents](#) representing the Agency's current thinking on good clinical practice (GCP) and the conduct of clinical trials,

and including selected guidelines of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (“ICH”), as published in the Federal Register on May 9, 1997.

The PD should also be familiar with the various types of control groups, their relative advantages and disadvantages, and the ethical issues associated with each control type, as outlined in the FDA guidance [Choice of Control Group and Related Issues](#), published May 2001. Although directly applicable to FDA-regulated trials involving investigational drugs or biological products, many of the principles can be applied to clinical trials in general.

Additional Requirements

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for other requirements depending on the source of support/funding (e.g., Department of Justice (especially for research conducted within the Bureau of Prisons)).

14.3 Detection of Harm, Minimization of Risks and Mitigation of Potential Injuries through Study Design and During the Course of the Research

Researchers design studies in a manner that minimizes risks to participants. (AAHRPP Element III.1.C)

Risks may affect physical, psychological, social, legal, or economic well-being, including loss of privacy or breach of confidentiality. The PD must minimize risks at all times by using procedures that are consistent with sound research design and that do not expose participants to unnecessary risks, and whenever appropriate, by using procedures already being performed on the participants for diagnostic or treatment purposes.

When submitting a Protocol Application to the IRB, the PD must:

- Describe the potential risks.
- Include, where possible, a scientific estimate of their frequency, severity, and reversibility. If statistical incidence of complication and the mortality rate of proposed procedures are known, this data should be included.
- Explain how risks will be minimized.
- Justify the level of risk.
- Describe adequate provisions for monitoring the data during the conduct of the research to minimize risk to participants (see [Chapter 9.2](#)).

For proposed changes to the research, including any change to mitigate potential harm to participants, the PD must submit a protocol Modification to the IRB describing any resulting changes in the level of risk to participants, and explaining the risk level and potential benefits.

For studies requiring Continuing Review, the PD must indicate whether there has been an increase, no change, or a decrease in the level of risk of the study. If the risk assessment has changed the PD must update the information in the Risks section of the protocol.

All studies considered more than low risk must include a data and safety monitoring plan which describes how the PD will oversee the participants' safety and welfare and how unanticipated problems involving risks to participants or others, and adverse events will be characterized and reported.

See also:

- [Evaluating Sound Study Design](#) [GUI-17]
- [Data and Safety Monitoring](#) [GUI-P20]
- [Other Federal Agencies - Additional Requirements](#) [GUI-42]
- [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13]
- [Chapter 9](#) (measuring and minimizing risks to participants)
- [Chapter 14.2](#) above (sound study design)
- [Chapter 15.2](#) (Protocol Director responsibilities in assessing and reporting events).

14.4 Recruitment

The IRB has and follows written policies and procedures to evaluate the equitable selection of participants. (AAHRPP Element II.3.C)

The IRB has and follows written policies and procedures to review proposed participant recruitment methods, advertising materials, and payment arrangements and determines whether such arrangements are fair, accurate, and appropriate. (AAHRPP Element II.3.C.1)

Researchers and Research Staff recruit participants in a fair and equitable manner. (AAHRPP Element III.1.E)

PDs are referred to the Stanford recruitment policies and procedures set forth in [Chapter 10.2](#).

The PD must provide all necessary information on the protocol application to allow meaningful review by the IRB of the recruitment process. See [Chapter 10.1](#).

The PD is instructed to follow [Recruitment](#) [GUI-33], [Telephone Screening](#) [GUI-15] (which includes phone script samples), and [Advertisements](#) [GUI-16], and the Human Subjects Research [website](#).

In selecting a population from which to draw participants for a particular research protocol, the PD must consider whether the choice of population results in an equitable distribution of the burdens and benefits of research. The PD must provide appropriate justification in the protocol application when recruiting participants among vulnerable populations such as prisoners,

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economically and educationally disadvantaged, individuals with impaired decision-making capacity, and people experiencing homelessness. (45 CFR 46.111(a)(3); 21 CFR 56.111(a)(3))

VA Research

During the recruitment process, making initial contact with potential participants in person or by letter prior to initiating any telephone contact, unless there is written documentation that the participant is willing to be contacted by telephone about the study in question or a specific kind of research as outlined in the study. If existing information from sources such as a medical record or database (research or non-research) are used to identify human participants, there must be an IRB-approved waiver of HIPAA authorization for this activity in the new protocol. Any initial contact by letter or telephone must provide a telephone number or other means that the potential participant can use to verify that the study constitutes VA research. If a contractor makes the initial contact by letter, the VA investigator must sign the letter. NOTE: This section does not apply when a Veteran calls in response to an advertisement.

See [VHA Directive 1200.05](#) for Telephone Contacts with Subjects.

Employees and Stanford University students

While employees and students are not vulnerable subpopulations per se, they may perceive that they are under some pressure from their superiors to agree to participate. PDs must provide a rationale for involvement of employees or students at Stanford University. When students are involved, the PD must explain:

- How they will be protected from coercion and undue influence, and
- What alternatives exist to participation.

Additionally, PDs are directed to the Research Policy Handbook RPH 5.5 [Use of Employees or Laboratory Personnel as Research Subjects](#) for policy on the use of employees or laboratory personnel as research participants.

Including Children as Participants

Children should be included in research, along with adults, unless there is a compelling rationale for their exclusion. Research that limits enrollment to children is generally not appropriate unless:

- i. The condition or disease is limited to children, or
- ii. The research seeks to obtain information on a test article or procedure that previously had been studied only in adults.

Appropriate Payment

Payments to research participants may not be of such an amount as to result in coercion or undue influence on the participant's decision to participate.

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Payments may not be provided to participants on a schedule that results in coercion or undue influence on the participant's decision to continue participation. For example, payment may not be withheld as a condition of the participant completing the research. If the participant withdraws early, payment must be prorated to reflect the time and inconvenience of the participant's participation up to that point.

See [Payment – Ethical Considerations](#) [GUI-39].

Additional Requirements

Additional requirements might apply, depending on the source of support/funding (e.g., Department of Defense, Department of the Navy, Department of Justice): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].

14.5 Human Research Protection Resources

Researchers determine that the resources necessary to protect participants are present before conducting each research study. (AAHRPP Element III.1.D)

Protocol Directors (PDs) are required to indicate in the Protocol Application whether they will have access to adequate resources to carry out the research. Resources, including space, personnel, services, and equipment required for conducting the proposed research properly and safely, must remain available as needed throughout the research. The PD must provide information about the qualifications and number of study staff, personnel training, available facilities, the time available to conduct and complete the research, and must demonstrate sufficient access to a population allowing recruitment of the required number of participants.

PDs should continually monitor the resources allocated for their research and notify the IRB if any change in the availability of resources may adversely impact the rights and welfare of participants.

In addition to IRB approval of the protocol, human participant research (including recruitment and enrollment) which is sponsored cannot begin until a contract has been finalized, or a grant award activated. See Research Policy Handbook RPH 13.1 [Gifts vs. Sponsored Projects and Distinctions from Other Forms of Funding](#).

For research that does not otherwise undergo scientific review, the Division Chief, Department Chair, School Dean or their designee must provide review of the scientific and scholarly validity of the proposed research. A [Review of Scientific and Scholarly Validity](#) must be completed and submitted to the IRB, as a condition of protocol approval. This requirement does not apply to minimal risk retrospective chart reviews.

Student projects (with student PDs) and department or gift funded research involving human participants (including recruitment and enrollment) cannot begin until the appropriate Division Chief or Chair of the PD's department in the School of Medicine, or the Dean or designee of other schools, has confirmed there are adequate resources to complete the study. If a study

has an academic sponsor, that sponsor is responsible for research oversight and must complete and submit an [Academic Sponsor – Review of Scientific and Scholarly Validity and Oversight](#) to the IRB, as a condition of protocol approval.

Submission of the Scientific and Scholarly Validity form or the Academic Sponsor form is not required for minimal risk retrospective chart reviews.

See also [Chapters 1.7](#), [2.3](#), [9.1](#), and [VHA Directive 1200.05](#) for additional Investigator Responsibilities.

14.6 Consent Process

Researchers employ consent processes and methods of documentation appropriate to the type of research and the study population, emphasizing the importance of comprehension and voluntary participation to foster informed decision-making by participants. (AAHRPP Element III.1.F)

Also see [Chapter 12](#) on informed consent and assent.

Informed Consent is a Continuing Process

Informed consent is a continuing process whereby the investigator and research participant have an on-going dialogue about all aspects of a research study that might inform a participant's decision to take part in the study, and their decision to continue their involvement as a participant. Although consent is given it may be withdrawn at any point. The informed consent process should be regarded as continuing throughout the duration of the research. The purpose of the consent process is to assure knowledgeable decision-making and voluntary participation.

This process generally includes:

- Bringing the research study to the notice of potential participants.
- Presentation and explanation by the investigator (or delegate) of the study and study activities to the participant or their legally authorized representative (LAR).
- Documentation of informed consent via a signed and dated written consent document.
- Ongoing discussions between the investigator and the participant regarding continued participation in the study.

The PD is expected to be familiar with:

- The informed consent policies in [Chapter 12](#), including the criteria for a legally effective informed consent process, and any additional federal, state (California), VA-specific (per [VHA Directive 1200.05](#)), and institutional requirements.

- Additional requirements might apply depending on the source of support/funding (e.g., Department of Defense, Department of the Navy, Department of Justice): see [Other Federal Agencies - Additional Requirements](#) [GUI-42].
- The consent process information and consent form templates provided on the Human Subjects Research website [Informed Consent - Medical](#) and [Informed Consent - Nonmedical](#) pages. The basic and possible additional consent requirements, and those specific to certain types of research activity (such as genetic testing, data and tissue repositories, and xenotransplantation), are addressed in [Chapter 12.1](#).

Consent requirements for research involving vulnerable and other special populations - including consent from a legally authorized representative (LAR) – are described in [Chapter 12.2](#). This addresses individuals with impaired decision-making capacity, prisoners, children, fetuses and neonates, and Stanford employees and students.

The Consent Document

The [Human Subjects Website](#) provides consent form templates, including VA specific templates, which address the required elements of informed consent, as well as providing language for other situations, (such as MRI, tissue banking), in which certain additional information may need to be disclosed to participants. For research involving children, an [Assent Template](#) is also provided.

To assist PDs in preparing consent documents comprehensible to lay persons (i.e., at approximately 8th grade level) a glossary of lay terms is also available on the [website](#).

The IRB encourages and recommends the use of a full consent form, translated into the participant’s language whenever possible. In certain situations, the use of a ‘short form consent process’ may be permitted by the IRB, incorporating the use of a short form consent document translated into the participant’s language. Templates of short form consent documents translated in a variety of languages and incorporating the basic required elements of informed consent are provided on the [Human Subjects Website](#).

In the event that the PD proposes to use a consent document based on one already developed by the sponsor or a cooperative multi-site research group, the PD is responsible for reviewing the existing document to determine if it fairly and adequately describes the research aims, procedures, risks, and benefits. The explanation of risks in the consent document should be based upon information presented in such documents as the protocol, the investigator’s brochure, any previous research reports, and, where applicable, the labeling for the drug or device.

If the research involves extensive screening procedures, the PD may wish to develop a separate consent document that explains the screening procedures in detail and provides a brief summary of the underlying research. In such circumstances, screening could begin after the individual signed the screening consent form but before the signing of the main consent

document, which would be signed only if the individual satisfied the screening criteria and was actually enrolled in the study.

See [Chapter 12.1](#) for detailed information on consent documents, the long form, and the use of the short form consent process.

Providing Consent Process Information to the IRB

In the Protocol Application, the PD must:

- Describe the consent process in enough detail to allow for meaningful review by the IRB,
- Include the proposed written informed consent document(s) that address(es) each of the elements of informed consent in the context of the research (unless the IRB waives the documentation requirement – see below), and
- Include any written material to be given to prospective participants to explain the nature of the research.

The PD is responsible for making all revisions to the proposed consent document as requested by the IRB. Any other change to the consent document must be submitted to the IRB for prior review and approval.

Requesting Waivers or Alteration of Consent Requirements

Under specific circumstances, the PD may request that the IRB grant a:

- Waiver or alteration of the consent process – i.e., the requirements for obtaining informed consent, or
- Waiver of documentation – i.e., the requirement to obtain a signature on a written consent document.

The requirements for these two options differ. Refer to [Chapter 12.5](#) for explanation.

Obtaining Informed Consent

The PD is responsible for obtaining and documenting the informed consent of individuals who participate in research, unless the requirement to obtain and document informed consent is altered or waived by the IRB.

No research procedures may begin until after the participant has signed the consent form, unless the IRB has approved a waiver or alteration of consent. Retroactive consent – i.e., consent obtained or documented after the participant has undergone one or more research procedures – is not acceptable.

The PD may delegate all or a portion of the informed consent process to others on the research team, such as co-investigators or research coordinators. However, it is ultimately the

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responsibility of the PD to ensure that those individuals carry out their tasks properly and in accordance with regulatory and IRB requirements.

The PD must use the consent document currently approved by the IRB. The IRB approval date must appear on (at least) the signature page of the consent document.

No participants should be involved in research prior to the IRB approval date, and no participants should be involved in research using a consent document whose approval period has expired.

The PD or their delegate should plan to discuss research with potential participants at a time when they are not under duress, and to allow sufficient time and opportunity to ask questions and to consider whether or not to participate in the research before agreeing to participate.

In discussing research with potential participants, the PD or their delegate:

- May not describe items or procedures under investigation as if they were known to be safe and effective as a treatment for the potential participant's disease or condition, or as if they present a known advantage,
- May not understate the risks of the research, as there may be no countervailing benefits to participants.

The PD or their delegate is responsible for giving the participant a copy of the signed informed consent document, and for maintaining the original form.

Obtaining Informed Consent in the Clinical Research Context - Special Considerations

The distinction between treatment and research is especially important if the PD is also the potential participant's attending physician, a situation that increases the risk of confusion. Thus, it must be clearly stated to the participant that they will be involved in research and that if randomization is involved, that this is also described.

The purpose of medical or behavioral treatment is to provide interventions designed solely to enhance the well-being of the patient or client. By contrast, research is designed primarily to develop generalized knowledge rather than to benefit each participant in the research. Research involves activities to test a hypothesis and draw conclusions, and any therapeutic benefit to the participants is secondary to the objectives of the research.

Research involving randomization of participants, whether to proven or experimental procedures, raises further issues. In these circumstances, the PD should ensure that each participant understands that the assignment will not be based upon the attending physician's clinical judgment as to which treatment may prove more beneficial to that participant and may involve additional testing that would not be performed as clinical care.

Posting of Clinical Trial Informed Consent Form

45 CFR 46.116(h) requires that for any clinical trial conducted or supported by a federal department or agency or the VA, one IRB-approved consent form must be posted by the lead Principal Investigator conducting the trial on a publicly available Federal website after recruitment closes and no later than 60 days after the last study visit by any subject. If the Federal department or agency supporting or conducting the clinical trial determines that certain information should not be made publicly available on a Federal Web site (e.g., confidential commercial information), such Federal department or agency may permit or require redactions to the information posted. More information on this posting requirement can be found on the [NIH website](#). Spectrum has [Informed Consent Form Disclosure guidance](#).

Consent Situations Requiring Prompt Reporting to the IRB

Situations where informed consent is not properly obtained or not documented, and no corresponding waiver or alteration of the consent process has been granted by the IRB, may constitute noncompliance. Such circumstances may require reporting to the IRB. These include, but are not limited to:

- Involving an individual in research without first obtaining their informed consent and a signed informed consent document (unless the IRB has explicitly waived these requirements).
- Involving an individual in research using a consent form other than the current IRB-approved form.
- Situations where the PD believes informed consent documents have been lost, misplaced, or destroyed.

See also:

- [Chapter 15.2](#) for information on reporting to the IRB
- [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13].

14.7 Response to Participants' Requests for Information and Complaints

Researchers and Research Staff have a process to address participants' concerns, complaints, or requests for information. (AAHRPP Element III.1.G)

Requests for Information

The PD and members of the research staff are required to respond promptly and adequately to all requests for information received from participants, prospective participants and their family members or designated representatives. In addition to providing information and answering questions that arise as part of the informed consent process, the PD must inform the participant that he/she is available to answer any questions that arise about the research in the future. The consent form must list the full name and contact information for the PD, and other research study staff as appropriate. The consent form must also inform participants how to

reach the IRB if they have any questions about their rights as research subjects (see Stanford University consent form template for contact information language).

Complaints

The PD is expected to investigate and respond promptly to complaints, and to follow the proper procedure for addressing and reporting complaints to the IRB. A complaint is a formal or informal, written or oral, expression of dissatisfaction by the participant or the participant’s representative. Complaints that are not resolved promptly by the PD or member of the research staff must be reported to the IRB as follows:

- Complete and submit a Report Form to the IRB
- Include with the Report Form a brief description of the complaint and the circumstances in which the complaint was made, and any action taken to date in addressing the complaint. Complaints are handled in accordance with the policies described in [Chapters 3.9](#) and [3.10](#).

If the complaint is not directly related to the conduct or design of the research, the IRB staff may refer the complaint to the appropriate Stanford institutional official or committee (e.g., as provided for in the applicable University or hospital policy on the handling of grievances.) In circumstances in which the complaint is referred, the IRB staff should provide the participant with the name and contact information for the referral.

On studies for which Continuing Review is required, investigators are required to list all complaints received about the research in the past year, whether or not they were previously reported to the IRB.

Privacy issues

If the complaint involves Stanford privacy practices, all documentation relating to the complaint must be retained for at least six years from the date of creation.

If such a complaint cannot be handled promptly, the appropriate Stanford Privacy Officer should be notified.

Ch. 15: Investigator Compliance

The protection of human participants in research is the shared responsibility of PDs, sponsors, and the IRBs; the PDs are ultimately responsible for the safety and welfare of participants. When conducting research with human participants, the PD agrees to, as part of the Protocol Application (Obligations section):

1. Design studies that are scientifically sound and that will yield valid results and conduct the study according to the protocol approved by the IRB
2. Be appropriately qualified to conduct the research and trained in Human Research Protection ethical principles, regulations and policies and procedures, and ensure all research personnel are adequately trained and supervised
3. Disclose to the appropriate departments any potential conflicts of interest
4. Report promptly any new information, modification, or unanticipated problems
5. Ensure that the rights of participants are protected, including privacy and confidentiality of data
6. Ensure that, when de-identified materials are obtained for research purposes, no attempt will be made to re-identify them
7. Apply relevant professional standards.

15.1 Qualification of Protocol Directors and Research Staff

Researchers and Research Staff are qualified by training and experience for their research roles, including knowledge of applicable laws, regulations, codes, and guidance; relevant professional standards; and the Organization’s policies and procedures regarding the protection of research participants. (AAHRPP Element III.2.A)

Training in the Protection of Human Subjects

Stanford requires that PDs and other personnel involved in the design or conduct of a project, including projects deemed to be exempt research under 45 CFR 46.104, confirm completion of training in the protection of human research participants. Individuals involved in the design or conduct of a project include investigators, nurse coordinators, senior professional staff, persons administering informed consent or surveys, post-docs, and students. Collaborating individuals operating under Stanford University’s FWA and third party (subcontract) research personnel or consultants must also comply with this education requirement.

Stanford employs the Collaborative Institutional Training Initiative (CITI) courses as its training program. Required CITI training for investigations includes, but is not limited to, modules on the history and ethical principles of human subject research, basic IRB regulations and review

process, informed consent, and research with vulnerable participants. Stanford requires a refresher training course to be completed every three years.

Good Clinical Practice (GCP) training is required, as applicable. Training is also available through the Stanford Clinical Research Operations Program, Office of Research Administration (ORA) Brown Bag sessions, webinars, and other resources provided by Stanford.

Completion of the required training is a condition for IRB approval of protocols and release of funds, regardless of the project's source of funding. During the review the IRB evaluates whether these requirements are met for each protocol event (new protocol, modification, and continuing review).

See also:

- [Chapter 1.6](#) Ethical and Legal Principles Governing Human Subject Research
- [Chapter 3.1](#) Policies and Procedures Available to Protocol Directors (PDs) and Research Staff
- [Chapter 4](#) Knowledge of Human Research Protection Requirements, for an outline of education provided for individuals responsible for human research, and description of the required training
- [Chapter 5.6](#) Sponsor-Investigator Research: Additional training is provided for investigators who have additional responsibilities as the research sponsor
- [Chapter 16.1](#) Agreement Includes Protection for Research Participants

Knowledge of Applicable Federal, State and Local Laws

The RCO disseminates and makes available to the Stanford research community,

- Via the [Human Subjects Website](#) and education programs, the following resources to promote knowledge about applicable Federal, State and organization policies for human subjects research: Human Research Protection Program policies
- Guidance on topics affecting the conduct of research, such as informed consent, vulnerable populations, conflict of interest, reporting requirements, etc.
- Template consent forms that include federal, state, and local requirements
- eProtocol System for protocol submission - with application questions intended to address required considerations
- Information and instructions on submitting protocols to the IRB
- References and links to federal, state, and organizational requirements
- Contact information for IRB staff for assistance

- The Stanford University [Research Policy Handbook](#) (RPH) is also available online, addressing topics such as RPH 1.9 [Retention of and Access to Research Data](#), and RPH 1.2 [Rights and Responsibilities in the Conduct of Research](#). RPH Chapter 5.8 focuses on [Human Subjects and Stem Cells in Research](#).

Where applicable, the California State laws have been included in the Stanford HRPP Policy Manual, for example, [Chapter 12.1](#) addresses informed consent requirements under the California Health & Safety Code. When Stanford investigators conduct research in states other than California, they are expected to be knowledgeable of and adhere to the laws of the state in which research is being conducted, as well as those of California. Investigators are advised to seek guidance from the IRB staff or Legal Counsel if they have questions as to the applicable laws.

Knowledge of the Definition of Human Subject Research

Researchers and Research Staff know which of the activities they conduct are overseen by the Human Research Protection Program, and they seek guidance when appropriate. (AAHRPP Element III.1.A)

Prior to submitting a protocol for IRB review investigators are instructed to consider whether their project meets the statutory definition of human subject research or clinical investigation. Step-by-step guidance is available to the investigators on the Human Subjects Research website: [Does My Project Require IRB Review?](#) This provides guidance based on DHHS- (OHRP), FDA-, and VA-specific requirements.

IRB staff is also available to assist investigators in determining if a project needs to be submitted for IRB review. If the proposed activity clearly does not involve "research" or "clinical investigation" and "human subjects", it does not require submission to the IRB. If there is any doubt as to whether an activity is human subject research, the investigator should [contact](#) the Research Compliance Office, or submit an [eProtocol application for the determination of Human Subject Research](#). See [Chapter 3.3](#) for additional information on the definition of human subject research.

15.2 Reporting to the IRB - Unanticipated Problems Involving Risks to Participants or Others (UPs), and Other Reportable Information

Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; Stanford policies and procedures; and the IRB's requirements. (AAHRPP Element III.2.D)

See also:

- [Chapter 3.10](#)
- [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13].

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PD Responsibilities

PDs are responsible for reporting unanticipated problems involving risks to participants or others (UPs) and other reportable information to the IRB. For industry sponsored projects, PDs are responsible for maintaining contact with the sponsor, and receiving reports from the sponsor, and if applicable, the monitoring entity (e.g., DSMB, DMC) and reporting suspected UPs and other reportable information to the IRB. For sponsor-investigator projects, the PD is solely responsible for reporting UPs and other reportable information to the IRB.

The IRB Report Form may also be used to report to the IRB events or information other than those required by regulation; these may be reported under item (7) in the Report Form, but PDs should consult with the IRB Panel Manager before reporting such items.

Routine, periodic reports (e.g., Data Monitoring Committee reports, annual progress reports) should be submitted to the IRB at Continuing Review. The IRB Report Form should **not** be used to submit these reports to the IRB.

Assessment by Protocol Director

The PD is responsible for the initial assessment of whether an event is a UP or other reportable information.

PDs must assess each event, whether received from a sponsor, monitoring entity or occurring on a sponsor-investigator project, and promptly report to the IRB, UPs and other reportable information according to [Events and Information that Require Prompt Reporting to the IRB](#) [GUI-P13]. (See flowchart [Process for Handling Reports](#).)

In all cases, UPs that are deaths or life-threatening experiences (at Stanford or when Stanford is the coordinating institution in a multi-site study), must be reported within 5 working days from when the PD learns of the event.

Reporting Assessed Events and Information

For events required to be reported to the IRB, PDs should submit reports using the online (eProtocol) Report Form. Adverse events that are deemed not to be UPs or other reportable information should be included in a narrative summary for the IRB at Continuing Review.

Reporting Timeframes

Type of event or information	Protocol has a monitoring entity in addition to, or other than, the PD	PD is the only monitoring entity for the protocol
UP that is a <i>death or life-threatening experience</i> , (at Stanford or when Stanford is the coordinating institution in a multi-site study)	Report to IRB within 5 working days** from when the PD learns of event.	
Other UP * (<i>not</i> death or life-threatening experience)	Report to IRB <i>within 10 working days**</i>	Report to IRB <i>within 10 working days**</i>
Reportable information** (items 2-6 in Events and Information that Require Prompt Reporting to the IRB [GUI-P13])	from when PD receives assessment from monitoring entity	from when PD learns of event or new information

* **VA research:** [VHA Directive 1200.05](#) and [VHA Directive 1058.01](#) detail research compliance reporting requirements for VA research.

** [Other Federal Agencies - Additional Requirements](#) [GUI-42] details research compliance reporting requirements for other federal agencies.

The IRB will review and assess the events and information reported and address them as described in [Chapter 3.10](#).

When Modifying the Protocol is Indicated

An event or new information might prompt a protocol modification – either initiated by the PD or specified by the IRB after reviewing a report. When an event or new information requires a modification to a previously approved protocol (e.g., new side effect in the consent form or suspension of enrollment) a modification must be submitted for IRB review and must be approved by the IRB prior to implementation of the proposed changes. The only exception to pre-approval is for modifications necessary to eliminate apparent immediate hazard to the research participants; in this case, the PD must submit the modification to the IRB within 5 days following its implementation.

Gene Transfer Protocols

The above information on reporting UPs and other reportable information also applies to gene transfer protocols. In addition, for these protocols, all injuries and serious adverse events

occurring at Stanford or at other participating institutions must be reported to the Biosafety Panel as outlined in the [NIH Guidelines](#) and the [Incident Reporting template](#).

15.3 Research Oversight

Researchers maintain appropriate oversight of each research study, as well as Research Staff and trainees, and appropriately delegate research responsibilities and functions. (AAHRPP Element III.2.B)

The general principles stated here apply to all research, including behavioral/social science research.

Oversight of Research Staff during Recruitment

The PD is responsible for ensuring recruitment activities, whether undertaken by research staff or the PD, are via methods set forth in the protocol application and approved by the IRB. The PD must ensure that informed consent is obtained from each research participant before that individual participates in the research study. The PD may delegate the task of obtaining informed consent to another individual knowledgeable about the research, while retaining ultimate responsibility over the conduct of the study.

Selection of Study Participants

The PD must ensure selection of study participants is equitable and appropriate to the goals of the study. Adequate safeguards for the protection of participants during the recruitment and conduct of research must be set forth in the protocol application. See:

- [Chapter 10.1](#) (equitable selection)
- [Chapter 14.4](#) (recruitment)
- [Recruitment](#) [GUI-33].

Informed Consent

PDs are responsible for assuring the quality of the informed consent process and for making sure that consent is obtained and documented before subject participation unless waivers are granted by the IRB. For a detailed discussion of the informed consent process requirements and description of available templates and guidance, see [Chapter 12](#).

For all research including VA Research:

If the investigator does not personally obtain informed consent, the investigator must delegate this responsibility in writing (e.g., by use of a delegation letter) to research staff sufficiently knowledgeable about the protocol and related concerns to answer questions from prospective participants, and about the ethical basis of the informed consent process and protocol.

If the investigator contracts with a firm (e.g., a survey research firm) to obtain consent from participants, collect private individually identifiable information from human participants, or be involved in activities that would institutionally engage the firm in human participants research, the firm must have its own IRB oversight of the activity. In addition, the Privacy Officer (PO) must determine that there is appropriate authority to allow the disclosure of individual names and other information to the contracted firm.

The investigator must ensure that all original or digitalized signed and dated informed consent documents are maintained in the investigator's research files, readily retrievable, and secure.

Study Conduct

Researchers and Research Staff follow the requirements of the research protocol or plan and adhere to Stanford policies and procedures and to the requirements or determinations of the IRB. (AAHRPP Element III.2.C)

The PD is responsible for conducting the study in a manner that is scientifically and ethically sound and for ensuring the use of appropriate methods and correct procedures, according to the approved protocol. Any new information, modification, or unanticipated problem involving risks to participants or others must be promptly reported to the IRB ([Chapter 15.2](#)), and research participants must be informed of any change that may affect their willingness to participate.

The PD will conduct the research activity in accordance with the terms of the IRB approval until any proposed changes have been reviewed and approved by the IRB, except when necessary to eliminate apparent immediate hazards to the subject.

The PD must assure that all personnel under his or her supervision are adequately trained and supervised and that research duties are delegated to individuals qualified to perform the assigned tasks. Any non-compliance must be reported promptly to the IRB as required in [Chapter 3.9](#).

The PD is also responsible for the timely and proper administration of the research project. Beyond the scientific and clinical conduct of the study, responsibilities include:

- Compliance with federal, state, and local laws and Stanford policies, including disclosure of any potential conflict of interest
- Adhering to the respective institutional Code of Conduct:
 - SHC/LPCH; Stanford University [Code of Conduct](#);
 - VAPAHCS Memo 151-15.01; Section 6.j (Responsibilities - Principal Investigator); [VHA Directive 1200.05](#).
- Fiscal management of the project

- Training and supervision of postdoctoral candidates, students, and residents
- Compliance with the sponsor’s terms and conditions (e.g., non-disclosure of sponsor confidential information)
- Submission of all technical, progress, financial, and invention reports on a timely basis
- Submission of modification and continuing review applications in a timely manner
- Obtaining approval for changes prior to implementation.

Compliance with the IRB

Federal regulations require that any research study involving human subjects be reviewed and approved by an IRB. IRB approval must be obtained before any recruitment or screening can take place.

It is the PD’s responsibility to submit a written protocol to the IRB for review. At submission, the obligations of the PD with respect to oversight of their research protocols and research staff during recruitment, selection of study participants, and conduct of the study according to the protocol as approved by the IRB are stated in the Protocol Application and must be agreed to by the PD for the submission to be accepted. The PD is responsible for ongoing adherence to the determinations and requirements of the IRB for the duration of the research.

The documents required for protocol submission are listed in [Chapter 8.1](#).

A detailed discussion of the roles and responsibilities of IRBs is presented in [Chapter 6](#).

Progress Report and Continuing Review Application

PDs must submit protocols (other than those subject to 45 CFR 46.104 - Exempt research) for continuing review by the IRB before the expiration date of the protocols, and in sufficient time to ensure the non-interruption of studies.

Final Report

At the conclusion of the study, PDs involved in research approved under regular review which enrolled participants must submit a final report to the IRB within 30 days.

Confidentiality of Records and Personal Data

PDs working with human subjects must safeguard the privacy of participants and protect the confidentiality of personal information:

- Safeguard mechanisms must be established, maintained, and documented throughout the research process
- Sustained attention must be paid to maintaining confidentiality of research data in the design, implementation, conduct, and reporting of research

- Full information about the privacy and confidentiality of data must be provided to prospective participants through the informed consent process
- Unintentional breaches must be avoided by taking additional precautions in communication, administration, and storage of information.

Privacy and confidentiality are addressed in [Chapter 11](#).

Privacy Rule (HIPAA)

When conducting research that involves the use and disclosure of protected health information (PHI), the PD must abide by the applicable HIPAA policy of Stanford and must be able to account for disclosures of PHI when an individual requests such accounting. See [Chapter 11.3](#), and Stanford University HIPAA Policy regarding [Patient Privacy](#).

Delegation of Research Responsibilities

PDs may delegate research responsibility. However, PDs maintain oversight and retain ultimate responsibility for the conduct of those to whom they delegate responsibility. The conduct of a study usually requires the involvement and contribution of other individuals under the direction of the PD, based on their qualifications and capabilities. In delegating study-specific tasks and responsibilities to other members of the research team, the PD must ensure that those assuming a duty are well trained and competent.

Additional Requirements

See [Other Federal Agencies - Additional Requirements](#) [GUI-42] for other requirements depending on the source of support/funding (e.g., Department of Justice, especially for research conducted within the Bureau of Prisons.) and [VHA Directive 1200.05](#) for VA research.

Student Investigators and Academic Sponsors

Student Investigators may assume PD responsibilities with the supervision and guidance of Academic Sponsors. In a study with an Academic Sponsor, the student investigator is the PD and has the following responsibilities:

- Design of the study
- Conduct of the study and all study-related activities
- Conduct of self and collaborators
- Protection of the rights and welfare of participants, including obtaining informed consent and maintaining privacy and confidentiality of data
- Proper application and reporting to the IRB
- Compliance with approved protocol

- Consultation with the Academic Sponsor and identification of protocol modifications warranted by unexpected events/circumstances.

Academic Sponsors are responsible for providing supervision and guidance to Student Investigators by:

- Overseeing study design and monitoring study conduct
- Ensuring that the student/staff investigator assuming duties are well-trained and competent
- Reviewing the protocol application prior to submission to the IRB
- Providing guidance in the protection of research subjects
- Assuring proper application and reporting to the IRB
- Working with student/staff investigator to identify modifications warranted by unanticipated problems or circumstances involving risks to participants or others.

The Academic Sponsor must confirm the scientific validity of the study and to his/her agreement to fulfill the above responsibilities. This [Review of Scientific and Scholarly Validity and Oversight](#) must be forwarded to the IRB before the protocol can be approved. See [Chapter 1.7](#).

Special Considerations for the Oversight of Research Protocols in FDA-Regulated Drug or Device Studies

FDA regulations and guidance specify the responsibilities of sponsors (and their investigators) using FDA test articles. [21 CFR 31 Subpart D; 21 CFR 812 Subparts C,E]. The FDA requirements are summarized in [Special Considerations for the Oversight of Research Protocols in FDA-regulated Drug or Device Studies](#) [GUI-26m].

In *sponsor-investigator research*, the PD assumes all of the responsibilities in overseeing the research normally assumed by sponsors in industry-sponsored projects.

15.4 Data Monitoring Plan (DMP)

Researchers and Research Staff follow reporting requirements during a research study in accordance with applicable laws, regulations, codes, and guidance; Stanford policies and procedures; and the IRB's requirements. (AAHRPP Element III.2.D)

When appropriate, the research plan makes adequate provision for monitoring the data collected to ensure the safety of subjects. (45 CFR 46.111(a)(6); 21 CFR 56.111(a)(6))

See also [Chapter 9.2](#).

The responsibility for human participant protection in human subject research is shared among the IRB, PD, trial sponsors and oversight boards or committees. The safety of participants must be considered in study design.

Studies that are more than low risk to participants must include a data monitoring plan (DMP) to evaluate whether the character, incidence, and severity of expected harms match those expected, and to evaluate the causality of unexpected harms. Requirements for a DMP are discussed in [Data Monitoring Plans](#) [GUI-P20]. Additionally, a description of the DMP is required in the Protocol Application submitted to the IRB. In order to approve research, the IRB determines that when appropriate, there will be adequate monitoring of data to protect the safety and well-being of participants.

Monitoring may be conducted by the PD, or a Monitoring Entity (ME). (See [Data Monitoring Plans](#) [GUI-P20] for examples of MEs.) In all studies, the PD has ultimate responsibility for identifying potential risks and identifying adverse events occurring in the study population and reporting the events to the sponsor and to the IRB as required in [Chapter 3.10](#).

For high risk studies, e.g., Phase I/II Cell and Gene Transfer Clinical Trials, there may be further discussion at a convened meeting to consider whether a DSM BOARD should be required, or if a robust DSM PLAN would be adequate, as described in [AID-59](#).

Sponsor Responsibilities

Sponsor responsibilities may include (but are not limited to), as appropriate to the scope and complexity of the research:

- Establishing procedures to assure that interim data remains confidential
- Notifying all participating IRBs of unanticipated problems involving risks to participants or others
- Notifying FDA and the responsible IRBs of any recommendations or requests made by a Monitoring Entity to the sponsor that address safety of participants.

If there is a Data Safety Monitoring Committee, sponsor responsibilities may include:

- Appointing a Chair
- Establishing procedures to assess potential conflicts of interest of proposed members
- Establishing Standard Operating Procedures (SOPs) for statistical analyses, report format, and meeting schedules
- Submitting SOPs to the FDA prior to interim data analyses, optimally before the initiation of the trial.

In sponsor-investigator research, the PD assumes all of the responsibilities in overseeing the research normally assumed by sponsors in industry-sponsored projects.

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Ch. 16: HRPP Coverage of Sponsored Research

Definitions for Chapters 16, 17, and 18

Sponsored research: Research funded by external entities through a grant or contract that involves a specified statement of work (e.g., the research proposal) with a related transfer of value to the sponsor, including clinical trials involving investigational drugs, devices, or biologics. (See Stanford University Research Policy Handbook, 13.3 [Specialized Categories of Sponsored Projects](#).)

Stanford sponsored research: Sponsored research conducted at Veterans Affairs Palo Alto Health Care System (VAPAHCS), Stanford University, Stanford Hospital and Clinics (SHC) and Lucile Packard Children's Hospital (LPCH) through a grant or contract with Stanford University. A "grant" is sponsored research that has few if any contractual terms other than those designating the research to be supported by the funding.

Palo Alto Institute for Veterans Research (PAVIR) sponsored research: Sponsored research conducted at VAPAHCS through a grant or contract between PAVIR and external sponsors.

VA research: Research conducted at VAPAHCS through Veterans Administration research awards.

16.1 Agreement Includes Protection for Research Participants

Stanford has and follows written policies and procedures setting forth the ethical standards and practices of the Human Research Protection Program. Relevant policies and procedures are made available to Sponsors, Researchers, Research Staff, research participants, and the Institutional Review Board, as appropriate. (AAHRPP Element I.1.D)

In Stanford and PAVIR sponsored research, Stanford University and PAVIR address the protection of research participants by:

- Including in their standard contract templates a provision that the sponsor acknowledges and understands that the Stanford HRPP is applicable to all human participant research. See:
 - Stanford University (Office of Sponsored Research (OSR)) [Clinical Study Agreement](#) template (Section 19),
 - Office of Technology Licensing (OTL) Sponsored Research (contact ico@stanford.edu), and
 - VA Cooperative Research and Development Agreement ([CRADA](#)) template (Human Subjects paragraph)
- Asking for the inclusion of such a provision in any proposed contract that does not use their standard templates

- Including in the cover letter accepting and acknowledging the grant an equivalent statement regarding the HRPP in grants to Stanford University.

Additionally, the IRB will review the proposed consent form and delete any provision that requires a participant to waive or appear to waive any legal rights (i.e., exculpatory provisions).

16.2 Provision Addressing Medical Care for Participants

Stanford has a written agreement with the Sponsor that addresses medical care for research participants with a research-related injury, when appropriate. (AAHRPP Element 1.8.A)

Stanford University, SHC and LPCH

In Stanford sponsored research, medical care for participants is addressed by:

- Including in its standard contract template a provision that the sponsor provides for the cost of diagnosis, care and treatment of any undesirable side effects, adverse reactions, illness or injury to a participant, without regard as to the fault of the sponsor (see Stanford University [Clinical Trials/Study Agreement](#) template (Subject Injury section))
- Asking for the inclusion of such a provision in any proposed contract that does not use Stanford University's standard template
- Including the substance of any such provision in the consent form (see Stanford University [consent form template](#))
- Including a statement in the consent form that participants do not waive any liability rights for personal injury by signing the consent form

VAPAHCS and PAVIR

In VA research at VAPAHCS, medical care for participants is addressed by complying with the applicable VA laws and policy that currently:

- Require pursuant to [38 CFR 17.85](#) that the VA provide free medical care to both veteran and non-veteran participants for those injuries, except for: (a) treatment for injuries due to noncompliance with study procedures, or (b) research conducted for VA under a contract with an individual or a non-VA institution
- Require pursuant to [38 USC 1151](#) that a participant who is a veteran be eligible for dependency and indemnity compensation for a qualifying additional disability or a qualifying death in the same manner as if such additional disability or death were service-connected, if the disability or death was not the result of willful misconduct and was caused by hospital care, medical or surgical treatment, or examination furnished to the participant and the proximate cause of the disability or death was

either; (a) carelessness, negligence, lack of proper skill, error in judgment, or similar instance of fault on the part of the department in furnishing the hospital care, medical or surgical treatment, or examination; or (b) an event not reasonably foreseeable

- Allowing pursuant to [28 USC 1346\(b\)](#) and [2671-2680](#) claims under the Federal Torts Claims Act for both veteran and non-veteran participants who consider the VA to be at fault for their injuries.

In research at VAPAHCS, PAVIR in its sponsored agreements addresses medical care for participants by:

- Abiding by the same laws and policy as specified above for VAPAHCS.

On behalf of VAPAHCS and PAVIR, the IRB requires that the VA Protocol Director include a statement in the VA consent form:

- Explaining the above-described possible benefits for participants, and
- Explaining that participants do not waive any liability rights for personal injury by signing the consent form. See VAPAHCS [consent form template](#).

Ch. 17: Communication from Sponsors Affecting IRB Oversight

In studies where Sponsors conduct research site monitoring visits or conduct monitoring activities remotely, Stanford has a written agreement with the Sponsor that the Sponsor promptly reports to Stanford findings that could affect the safety of participants or influence the conduct of the study. (AAHRPP Element I.8.B)

Stanford University and Palo Alto Veterans Institute for Research (PAVIR) have included in their standard sponsored research contract templates provisions that the sponsor will notify the Protocol Director or the IRB of:

- Non-compliance with the protocol or applicable laws, particularly those laws related to participants, that could impact the safety or welfare of the participants
- Serious adverse events that have been reported to the FDA or other governmental agency in relation to the protocol at Stanford or any other site
- Unanticipated problems in the protocol at Stanford D or any other site that could relate to risks to participating participants, and
- Circumstances that could affect participants' willingness to continue to participate in the protocol or the IRB's continuing approval of the protocol.

When non-standard contract templates are used, the sponsor is asked to include equivalent statements.

Data and Safety Monitoring (DSM) in sponsor agreements

When the Sponsor has the responsibility to conduct data and safety monitoring, Stanford has a written agreement with the Sponsor that addresses provisions for monitoring the data to ensure the safety of participants and for providing data and safety monitoring reports to Stanford. (AAHRPP Element I.8.C)

For sponsored research, Stanford agreements specify that, as appropriate:

- Provisions are made for monitoring study data which could affect participants' safety;
- The results of this monitoring are reported to the researcher (PD) so that:
 - Routine monitoring reports will be submitted as part of Continuing Review applications to the IRB, and
 - Urgent reports (those meeting the criteria in [Events and Information which Require Prompt Reporting to the IRB](#) [GUI-P13]) are submitted according to the guidelines specified in this same guidance.

Ch. 18: Knowledge Benefit and Participants' Interests

18.1 Publication of Research Results

Before initiating research, the Organization has a written agreement with the Sponsor about plans for disseminating findings from the research and the roles that Researchers and Sponsors will play in the publication or disclosure of results. (AAHRPP Element I.8.D)

Stanford University, Stanford Hospitals and Clinics (SHC) and Lucile Packard Children's Hospital (LPCH)

For sponsored research, Stanford University establishes the importance of disseminating research findings as one of its most important policies through its policy Openness in Research. See Research Policy Handbook RPH 1.4 [Openness in Research](#), which provides, in part: "That the principle of openness in research – the principle of freedom of access by all interested persons to the underlying data, to the processes, and to the final results of research – is one of overriding importance."

Stanford University requires that provisions for fair and reasonable ownership of data and research results be included in its sponsored research agreements and has a process that allows investigators to place their inventions in the public domain if that would be in the best interest of technology transfer and if doing so is not in violation of the terms of any agreements that supported or governed the work. See Research Policy Handbook RPH 9.1 [Inventions, Patents and Licensing](#).

In all sponsored research, Stanford University requires the dissemination of research results in a manner consistent with the above-referenced policy Openness in Research. A [project checklist](#) is used to implement this policy when reviewing research proposals, solicitations, award notices, non-disclosure agreements, and any other document related to sponsored research. This checklist is referred to from RPH 1.4 [Openness in Research](#).

Stanford University implements this policy in agreements concerning sponsored research by:

- Including in its standard contract templates a provision that provides the investigator with a right to publish the research results. See Stanford University [Clinical Trials/Study Agreement](#) template (Publication Section) and Stanford University Office of Technology Licensing (OTL) Sponsored Research (contact ico@stanford.edu).
- Revising any provision in any proposed contract that limits an investigator's right to publish research results in a manner that is inconsistent with the Policy on Openness in Research
- In grants: Including in the cover letter accepting and acknowledging the grant a statement of the applicability of the Policy on Openness in Research.

Veterans Affairs Palo Alto Health Care System (VAPAHCS) and Palo Alto Veterans Institute for Research (PAVIR)

For VA research and PAVIR sponsored research, VAPAHCS has policies that formally state that presentation of research results to the scientific community is an essential part of its research programs and that investigators are encouraged to publish and present the results from sponsored research at scientific and medical conferences. See [VHA Directive 1200.05](#)

Additionally, the VA retains ownership of all research data and results obtained from the use of resources provided by the VA as a result of conducting the research pursuant to federal law (35 USC 102 & 200-212, 37 CFR 501, and 38 CFR 1.650-1.663).

PAVIR abides by the above-described policies of the VA for its sponsored research at VAPAHCS, and also addresses the dissemination of research results by:

- Including in its standard contract template a provision that states that (a) PAVIR or any investigator may freely publish and disseminate the results of a clinical trial and (b) that the authorship and contents (including scientific conclusions and professional judgments) of any paper submitted shall be determined by PAVIR. See VA Cooperative Research and Development Agreement ([CRADA](#)) template (section 7.3 Presentations and Publications) template.
- Revising any provision in any proposed contract that limits an investigator’s right to publish research results in a manner that is inconsistent with its standard provision.

18.2 Communicating Study Results to Participants

When participant safety could be directly affected by study results after the study has ended, Stanford has a written agreement with the Sponsor that the Researcher or Stanford will be notified of the results in order to consider informing participants. (AAHRPP Element I.8.E)

When the IRB learns of events that could affect participant welfare after a study has closed (e.g., a drug studied at Stanford is withdrawn by the FDA), the IRB seeks information, deliberates, and considers whether (and how) to contact participants who might be affected. Even when the study is not yet closed, but participants have completed participation, the IRB or PD informs former participants when information is learned that could affect their welfare.

For sponsored research, Stanford University and PAVIR address communication with sponsors regarding the impact of research results on participant health and safety by:

- Including in their standard contract templates a provision that the sponsor will develop a plan of communication with the Protocol Director that is acceptable to the IRB when new findings or results of the protocol might impact the willingness of subjects to continue to participate in the protocol or directly affect their current or future safety or medical care, or by asking for the inclusion of such a provision in any proposed contract that does not use their standard template.

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See:

- Stanford University [Clinical Trials/Study Agreement](#) template (Human Research Protection Program section))
- Stanford University Office of Technology Licensing (OTL) Sponsored Research (contact ico@stanford.edu)
- VA Cooperative Research and Development Agreement ([CRADA](#)) template (section 7.3 Presentations and Publications

Ch. 19: Addressing Concerns of Research Participants

Stanford has and follows written policies and procedures that establish a safe, confidential, and reliable channel for current, prospective, or past research participants or their designated representatives that permits them to discuss problems, concerns, and questions; obtain information; or offer input with an informed individual who is unaffiliated with the specific research protocol or plan. (AAHRPP Element I.4.A.)

Researchers and Research Staff have a process to address participants' concerns, complaints, or requests for information. (AAHRPP Element III.1.G.)

Consent Form Requirements

The IRB requires that all consent forms include information on how to contact the investigator(s) conducting the research study. Participants are instructed to call the investigators if they have any questions about the research, or if they believe they have suffered a research-related injury. Each consent form must also include telephone numbers for the IRB (a local number and a toll-free number). The IRB contact information affords current or past research participants or their designated representatives a means to contact an informed individual who is independent of the research team about their rights as a research participant or other concerns. The IRB also serves as a conduit for receiving information from any party who is not satisfied with the manner in which a study is (or was) being conducted, or if any party has any concerns, complaints or general questions about research or the rights of research participants.

[Consent form templates](#), available on the Human Subjects Research website, include instructional text and verbatim language for the inclusion of the investigator's contact information and IRB telephone numbers under the consent form heading "Contact Information." The IRB's physical address is included in the consent form template to also allow for written communication.

Recruitment Material Requirements

The IRB requires specific contact information to be included in participant recruitment materials – flyers, newspaper ads, newsletters, and web postings. [Advertisements: Appropriate Language for Recruitment Material](#) [GUI-16] provides appropriate language to include in recruitment material.

All recruitment materials must include the appropriate contact information for the investigator(s) conducting the study. The IRB reviews all recruitment materials, and the addition of IRB contact information is required when appropriate.

Telephone (Screening) Scripts

The IRB requires investigator and IRB contact information be included in telephone scripts. Telephone scripts are often used to screen prospective participants. Like the consent forms, telephone scripts must include telephone numbers for IRB (a local number and a toll-free number), as well as telephone numbers for the investigators. This contact information provides prospective participants with channels of communication to the investigators and the IRB for questions, concerns, input, information, or complaints.

Responding to Contacts from Participants or Others

Prospective Participants

Calls from prospective participants interested in medical research are generally forwarded to [the appropriate medical department](#) for follow up with the interested caller. Calls from prospective participants interested in nonmedical research are generally received and handled by the IRB 2 (Nonmedical) Manager.

All other contacts are referred to the IRB Senior Advisor.

Participant Concerns

Concerns of research participants are followed up by the IRB Senior Advisor who calls the individual to gather more information. As appropriate, concerns may be forwarded to the IRB 2 (Nonmedical) Manager. Minor concerns are generally resolved by a phone call.

More complex concerns are followed up by the HRPP Associate Director with the relevant IRB Chair and others in the Research Compliance Office.

Website

The Human Subjects Research [website](#) includes participant outreach information addressing the general rights of research participants and provides links to various research resources. Additionally, the website has a toll-free number listed for participants to ask questions, offer input, raise concerns or complaints about research, a research related injury, or any question about the rights of research participants.

The Office of General Counsel also has instructions to forward callers seeking human research information to the HRPP Associate Director in the RCO.

Ch. 20: Education and Outreach

Stanford employs several mechanisms for communication and education to increase public awareness and educate potential research participants.

20.1 On-line Resources and Educational Materials

Stanford conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement. (AAHRPP Element I.4.B.)

Human Subjects Research website

The Human Subjects Research website contains:

- The [For Participants](#) page which provides information and resources about participating in research for participants, prospective participants, and community members, including:
 - Frequently asked questions (FAQs)
 - Link to a [listing of current clinical trials](#) taking place at Stanford Definitions of research terms (e.g., clinical trials, including the various phases and informed consent)
 - General information on the rights of research participants and questions to ask before agreeing to participate in research
 - Links to OHRP brochures: [Becoming a Research Volunteer](#): It's Your Decision (in English and Spanish)
 - Links to entities and organizations where research information can be obtained (e.g., National Cancer Institute, FDA and OHRP)
 - Contact information for inquiries about current research at Stanford
 - Link to the Circle of Supporters of the Center for Information and Study on Clinical Research Participation (CISCRP) [website](#) (see below.)

Association for the Accreditation of Human Research Protection Programs (AAHRPP)

AAHRPP is an independent, non-profit accrediting body, ensuring that accredited programs, such as the Stanford Human Research Protection Program (HRPP), meet rigorous standards for quality, participant protection, and ethically sound research.

Information about accredited programs, and about being a research participant, is available on the [AAHRPP website](#).

Circle of Supporters of the Center for Information and Study on Clinical Research Participation (CISCRP)

Stanford is a member of [CISCRP](#), a nonprofit group dedicated to educating and informing the public, patients, medical/research communities, the media, and policy makers about clinical research participation.

Stanford Cancer Institute

The Stanford Cancer Institute publishes a newsletter and maintains a research-related website that promotes public awareness and participant education. See the Stanford Cancer Institute website [Outreach Programs](#). It also offers prospective participants [information](#) on available research opportunities and other research related topics.

Other Stanford Resources

- Other departments at Stanford provide web-based information on current research opportunities (e.g., Bipolar Disorders Clinic, Stanford Prevention Research Center)
- The [Stanford Health Library](#) is a free public consumer health information library that provides scientifically based medical information to help people make informed decisions about their health and their health care. The Health Library is a community service of Stanford Hospital and Clinics (SHC)
- The [Stanford Mini Med School](#), available to the general public, features more than thirty scientists and physicians from the School of Medicine, and offers a dynamic introduction to the world of human health and the groundbreaking changes taking place in medical research and health care today. Significant parts of the course are [available online for free](#)
- The **Veterans Health Administration** offers information on a variety of [research topics](#).

20.2 Participant Research Inquiries

Stanford conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement. (AAHRPP Element I.4.B.)

Participant inquiries about clinical studies received by the RCO and Stanford Center for Clinical and Translational Education and Research (Spectrum) are referred to the appropriate department.

The Human Subjects website [For Participants](#)

<https://researchcompliance.stanford.edu/panels/hs/forms/for-participants> summarizes resources for obtaining information and contacting appropriate individuals/offices, including the Spectrum resource page [Patients & Community](#).

20.3 Outreach

Stanford conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement. (AAHRPP Element I.4.B.)

- [Center for Information and Study on Clinical Research Participation \(CISCRP\)](#) – The Research Compliance Office and Stanford researchers participate in the [AWARE for All](#) program – Clinical Research Education Days. These educational programs are held in metropolitan areas and are free and open to the public. They include thank you receptions for local clinical research participants, informational workshops with renowned physicians and researchers, health screenings and additional educational resources. (See CISCRP [website](#))
- [Spectrum](#) administers Research Match, a website to bring together people who are trying to find research studies, and researchers who are looking for people to participate in their studies. The [Research Match](#) registry is free and secure, and anyone can join.
- [Office of Community Engagement \(OCE\)](#) supports informed, committed, and sustained community engagement in local health issues.
- [The Stanford Health Library](#) is sponsored by Stanford Hospital & Clinics and provides scientifically-based free health and medical information.
- [Stanford Continuing Studies](#) often offers courses and sponsors free public events covering the life sciences and related topics.
- Clark Center Lectures: The [Bio-X Program](#) supports, organizes, and facilitates life bioscience interdisciplinary research by successfully bridging the disciplines of biology, medicine, engineering, computation, and physics to advance biomedical knowledge. The James H. Clark Center is the hub of Bio-X, and a variety of events are hosted at the Center. These events are open to the public. Some major programs are Bio-X Interdisciplinary Initiatives Symposium; Bio-X Frontiers in Interdisciplinary Biosciences; Bio-X Annual Symposia; and Bio-X Fellows Symposium.

20.4 Evaluation

Stanford conducts activities designed to enhance understanding of human research by participants, prospective participants, or their communities, when appropriate. These activities are evaluated on a regular basis for improvement. (AAHRPP Element I.4.B.)

Evaluations take place in an ongoing manner. The various organizations cited in the previous sections of this chapter evaluate their impact on an ongoing basis. For instance, course evaluation surveys are routinely used as part of Stanford's Continuing Studies courses; Spectrum has a Tracking and Evaluation Program (and in a recent study performed by Spectrum over 1000 past research participants were asked to respond to a comprehensive survey);

CISCRP conducts surveys regarding public opinion on clinical research on a regular basis, and makes their [survey results available](#).

All IRB staff, members and Chairs are requested to report both positive and negative feedback about all HRPP outreach activities, (wherever the feedback originates), to the IRB staff, who track this input in order to make changes to improve outreach activities.

20.5 Community Participation in Research

Stanford promotes the involvement of community members, when appropriate, in the design and implementation of research and the dissemination of results. (AAHRPP Element I.4.C)

For certain types of studies, it might be appropriate to involve individuals from the community in which the research will take place, in the design and conduct of the research. Stanford University supports and facilitates such community participation through a number of initiatives which address community-based issues, and by supporting researchers with programs that address issues of importance to the community in which we operate. These efforts may involve close collaboration with constituent communities and interest-groups.

Information for the community at large and potential research participants is available on numerous websites supported by the University, and informational literature is distributed locally to community organizations, clinics, and other locations.

As appropriate to their study, researchers are encouraged to contact resources at Stanford for information on engaging and involving the community in research.

Stanford Resources

Stanford resources include:

- The [Office of Community Engagement](#) (OCE): Builds opportunities for substantive community engagement among medical, graduate and undergraduate students; supports and develops faculty engagement in community health; promotes the translation and dissemination of scholarly work on health issues affecting local communities; and responds to community-health related needs and inquiries from students, faculty, health professionals and members of the surrounding community. The objective of the Office of Community Engagement research program (OCE) is to establish and promote a new culture in which community engagement and the translation of research findings from the bedside to the community, and the flow of new research questions from the community back to the investigators, are key components of success.

To reach this objective, OCE works to:

- Strengthen community partnerships and facilitate two-way communication on research goals by providing a single point-of-contact for community

groups, achieved in part by collaboration between the office and a broadly representative community advisory board.

- Build the capacity for community-based outcomes research at Stanford by providing staff support, expert consultation, and training.
- Integrate faculty and staff who have expertise in community-based and outcomes research into the [Center for Innovative Study Design](#) (CISD).
- Create systems to facilitate research partnerships that will increase the diversity of research participants represented in our clinical studies.
- Promote active dissemination of research results by using existing partnerships, shared clinical information systems, and experience in implementation science to effectively translate and incorporate new evidence-based science into clinical practice.

Community-based participatory research is not limited to the School of Medicine but may involve collaboration between the Stanford University Schools – for example, research on obesity prevention involving faculty of the School of Medicine and the School of Education.

Additionally, the OCE uses resources of the [Community-Campus Partnerships for Health](#), and works with a number of [community partner](#) organizations such as free clinics, local schools and school districts, community health centers, and advocacy programs.

- An annual [Community Health Symposium](#) organized by medical students highlights and disseminates student work in the community, co-sponsored by OCE and the Stanford Center for Clinical and Translational Education and Research ([Spectrum](#))
- [Stanford Prevention Research Center](#) (SPRC): Conducts interdisciplinary research into the determinants of chronic disease; develops community-based prevention strategies.
- The [Center for Innovative Study Design](#) (CISD): Provides support in study design or access to other useful resources for investigators involved in community-based research.
- [Scholarly Concentration in Community Health](#): This is a School of Medicine required course for first year medical students, involving research carried out in partnership with community organizations.
- [Population Health Sciences Initiatives](#): The aim of the program is to achieve the “translation” of new technologies and therapies from the laboratory to the patient and community. The [Stanford Prevention Research Center \(SPRC\)](#), [Primary Care and Outcomes Research Center \(PCOR\)](#), and [Biomedical Informatics Research Center \(BMIR\)](#), are among the world’s leaders in population based research. To promote

the success of this initiative, the department has created a new [Quantitative Sciences Unit](#) comprised of biostatisticians and data analysts and an expanded program of contemporary clinical epidemiology linked to clinical genomics. These programs, along with existing programs in SPRC and [General Internal Medicine](#), form the core of the new [Center for Population Health Sciences](#).

- [HAAS Center for Public Service](#) - Community-Based Research Fellows Program: Supports teams of faculty, students, and community partners in conducting research that addresses community-identified research needs.
- Under the [Office of the Vice Provost and Dean of Research](#), the [Freeman Spogli Institute for International Studies' Center for Health Policy \(CHP\)](#), and the [School of Medicine's Center for Primary Care and Outcomes Research \(PCOR\)](#) - operating under the joint working name of Stanford Health Policy - conduct multidisciplinary research into critical health policy and health-care delivery issues. Community stakeholders are included, for example, when:
 - Stanford Health Policy promotes interaction among leading researchers, clinicians, healthcare executives, policymakers, and members of the public by hosting seminars, lectures, and roundtables. These forums provide vital opportunities for the health policy community at Stanford and in the San Francisco Bay Area to share ideas and expertise.
- [School of Education](#): Supports various programs and projects affecting the local and broader communities. For example:
 - The [John W. Gardner Center for Youth and Their Communities \(JGC\)](#) partners with communities to research, develop, and disseminate effective practices and models for developing well rounded young people. The [Stanford Center for Opportunity Policy in Education \(SCOPE\)](#) partners with a local high school to showcase a teacher-led redesign effort to other school and school district leaders (administrators, principals, teachers, school board members, and parent leaders).
- School of Humanities and Sciences: Within this school:
 - The [Institute for Research in the Social Sciences \(IRiSS\)](#) is home to the [Research Experience Program \(REP\)](#), a mutually beneficial research collaboration between Stanford University and local community colleges. The REP enriches the student experience by allowing community college students to participate in social science research projects, and gain exposure to the research process, as well as also expanding the pool of research subjects available for Stanford researchers, enabling them to conduct more robust and timely experiments. Participating community college instructors are designated as Affiliates of [IRiSS](#) and invited to participate in IRiSS events held at Stanford.

Considerations for IRB Review

In addition to applying all relevant federal, state, and local regulations and Stanford policies, when reviewing such research, the IRB may consider the following, as pertinent to the type of research proposed:

- The appropriate community, and community representatives have been identified
- The research plan involves collaboration and communication between researchers and community in research design, conduct, and dissemination of results as appropriate
- It is recognized that the design and conduct of each phase of the research may be a somewhat iterative process, as researchers and community members gain knowledge and familiarity with the process
- Additional expertise will be called upon as needed to provide input on cultural or local context, or other special circumstances
- In addition to traditional research publication routes, results will be disseminated in ways that are accessible and intelligible to the community involved in the research
- Possible impacts of the research on the community beyond the life of the current project are addressed.

Ch. 21: Emergency Preparedness and Response

Stanford has and follows written policies and procedures specifically designed to protect the rights and welfare of research participants during an emergency. (AAHRPP Element I.1.H)

This policy prepares the research community for emergencies that may affect the conduct and operations of human research. The plan focuses on the rights and welfare of research participants and the continuity of research. It is to be used in conjunction with [the Stanford University Emergency Plan](#) which provides instructions to Principal Investigators/Protocol Directors and others on topics such as lab and workplace safety. In an emergency, Stanford personnel are to go to <https://emergency.stanford.edu> and their department plans for instructions. This policy applies to human research protections not otherwise covered by Stanford University Emergency Plan, departmental, and lab emergency plans. Health and wellbeing of faculty, staff, students, research participants, and others is first and foremost priority.

21.1 Types of Emergencies

Procedures will vary depending on the nature and severity of the emergency and whether studies provide a direct benefit to participants or can apply alternatives to in-person activities. Emergencies may be:

- a. Widespread infectious diseases (e.g., pandemics, regional outbreaks).
- b. Extreme weather events, natural or human-caused disasters (e.g., fires, earthquakes).
- c. Systems, networks, website, and power outages or threats.
- d. Infrastructure damage (e.g., buildings, water).
- e. Accidental or intentional chemical, biological, radiologic, and nuclear threats.
- f. Public disturbance involving acts of violence (e.g., protests, active shooter, etc.).

21.2 Responsible Parties

- a. The Institutional Official, Research Compliance Office (RCO) Director, IRB Chairs, and/or their designee implement an emergency plan for the HRPP.
- b. Policy Lead and/or staff in Continuous Quality Improvement periodically evaluate the plan.
- c. Policy Lead and/or staff in Continuous Quality Improvement educate the research community on HRPP emergency preparedness.
- d. RCO emergency response team follows guidance and directs others with regard to on-campus safety.

21.3 Assessing Impact and Potential Actions

Stanford's Institutional Official, RCO Director, and/or IRB Chairs along with other senior RCO staff will assess the potential damage and impact of the event to the HRPP. Some emergencies may be local and activities can be moved online, off campus, or to other IRBs. Other emergencies may have broader impact and may require temporary suspension of some or all of research. Stanford prioritizes research and will maintain activities as much as possible. Facilities will consider the impact of operations when there is loss to physical buildings, other infrastructure, and networks.

Potential actions regarding the conduct of human research activities during an emergency include:

- a. Allowing continuation of studies that do not pose risk to participants (e.g., online research activities, activities off-site, etc.).
- b. Postponing the implementation of certain types of studies (e.g., in-person studies with minimal benefit to participants).
- c. Restricting recruitment or enrollment for certain studies, while allowing activities to be continued on existing participants.
- d. Revising current studies to allow for alternate activities (e.g., remote study visits, conference calls, or video conferencing). Some activities may occur without revision such as screening procedures mandated by the health care system (e.g., COVID-19 hospital protocols).
- e. Processing continuing reviews, research related to the emergency, and therapeutic studies would take priority over review of other studies during limited review capacity.
- f. In an extreme situation, Stanford may shut down all research temporarily.

21.4 Continuity of Human Subjects Research and IRB Review

Continuity of operations and IRB review for the infrastructure in the HRPP may include:

- a. eProtocol system and RCO servers have a secondary back-up system and secondary servers and are all continuously backed up at Stanford's Disaster Recovery environment. This environment houses critical administrative and business systems in support of the University's business continuity efforts. The operational data are in multiple locations including the cloud and available to RCO staff. If the primary eProtocol system is down for an extended period, Stanford has the backup system to submit urgent continuing reviews, revisions, and reports and for members to enter reviews. Stanford will work with IT to restore critical computer systems. Trained UIT personnel handle the disaster recovery (DR) process. The DR sites are periodically tested to ensure they are functional, have recent data restored, and can be accessed. University IT constantly monitors Stanford's network and employs mitigation strategies. In the event of damage to offices, RCO will have personnel

work remotely. Meetings will be held electronically. Paper records have electronic back up in case of water or fire damage.

- b. Stanford has [minimum-security standards](#) for systems and servers to protect against cybersecurity threats including ones built and deployed by partners and vendors (e.g., eProtocol, Adobe Sign, REDCap, etc.).
- c. If some RCO personnel are unavailable, duties will shift to keep business operations intact by other trained staff.
- d. RCO and the IRB will determine, based on assessment of event, if certain activities will be recommended to implement as alternatives for safety immediately while allowing them to be submitted in a future revision. These activities (e.g. switching from a scheduled in-person follow-up visit to a telehealth visit during the beginning of a pandemic) will be discussed with study staff and may be communicated on the RCO website.
- e. IRBs may add ad hoc meetings to accommodate volume.
- f. The RCO has developed a Business Continuity Plan with the Vice Provost and Dean of Research, which designates RCO systems and processes as critical to University functions.
- g. For onsite staff, the RCO has a building emergency response plan.

21.5 Research Continuity

- a. Researchers are to follow the Stanford University Emergency Plan and their own departmental plans to prioritize lab and workplace safety.
- b. Investigators can prepare for emergency events by including flexibility for virtual enrollment, electronic consent, and virtual visits in their protocols.
- c. Investigators may implement changes to approved research prior to IRB review and approval if necessary to eliminate apparent immediate hazards to the subject.
- d. If in-person research is restricted, Protocol Directors must assess the need for activities that protect participants' safety and well-being, such as collecting information online or by phone and following the sponsor and investigational pharmacy instructions on alternatives (e.g., different research sites, home administration by qualified research personnel, home delivery). The research staff should contact the IRB on how to proceed. Other activities must be assessed to see if information can be collected online or by phone.
- e. When deviations occur (e.g., participant unable to attend an in-person visit), the Protocol Director must track such events to report to FDA or other regulators, if applicable, and to report noncompliance.
- f. Researchers must keep participant and study team contact information current for long-term studies to provide emergency information as necessary.
- g. Storage, handling, and control of drugs and medical devices are maintained during an emergency per FDA guidance.
- h. Investigators must plan for how biospecimens repositories are protected during disasters (e.g., use of backup generators during loss of electric power).
- i. Stanford will provide security of research facilities during emergencies as able.

21.6 Reliance on Other IRBs

In an emergency, Stanford may rely upon other organizations for IRB review. Stanford has reliance agreements with Advarra, WCG IRB, and is a SMART IRB participant that allows reliance with over a thousand other institutions.

21.7 Education and Training

IRB staff will read the RCO Emergency Preparedness Plan. IRB members and staff will read this policy to understand their role during emergencies with respect to human subjects research. Protocol Directors read the Stanford University Emergency Plan and their department, building, and lab plans along with this policy and ensure that the study team are aware of such plans. Incident specific materials may be developed at the beginning of the emergency for distribution.

Stanford personnel must complete the online course General Safety, Injury Prevention (IIPP), and Emergency Preparedness (EHS-4200). Stanford personnel should familiarize themselves with educational resources at the [Cardinal Ready](#) website and sign up for Stanford's AlertSU emergency notification system. Researchers working at Stanford Children's Health (SCH) must complete annual hospital health and safety training assigned in HealthStream.

21.8 Notification and Incident Response from the HRPP

RCO maintains a listserv of researchers on active IRB protocols, IRB members, staff, and institutional contacts (i.e. research pharmacy). RCO will inform via email that the emergency response plan has been activated and what researchers, members, and staff are expected to do. A contact phone number and email will be made available on the notification if other RCO contacts are unavailable. The notice will also be on the RCO homepage.

During an emergency, RCO should be contacted regarding continuing review, revisions, and reports, for active studies that need to be continued (e.g., therapeutic drug trials, etc.).

If a change was made without IRB approval to eliminate hazards, it must be reported to the IRB within 10 working days. There may be certain types of modifications that can be made without prior approval; RCO will communicate this and alternatives for reporting on the website.

RCO may communicate delay in reviews via the RCO website and/or email listservs. RCO will work with relevant departments, resources, and external vendors to ensure continuity of HRPP operations where possible.