

University of California, San Diego
Human Research Protections Program
Institutional Review Board
Standard Operating Policies and Procedures

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Section One: General Administration

Responsibility and Authority

Policy

In accordance with federal policy on the Protection of Human Subjects (DHHS Policy 45 CFR Part 46, FDA Policy 21 CFR Parts 50 and 56), the University of California, San Diego (UCSD) is responsible for the protection of the rights and welfare of human subjects in research conducted by, or under the supervision of, UCSD faculty, staff or students. In addition, UCSD provides review and monitoring services for the human subjects research conducted by investigators of the Veterans Administration San Diego Healthcare System (VASDHS), as an affiliated Institutional Review Board (IRB) under 38 CFR Part 16. To conduct this responsibility effectively, the University supports IRB committees that provide initial review and ongoing oversight of the ethical conduct and risks associated with research protocols involving human subjects. It is the responsibility of the IRBs to: 1) determine and certify that all projects reviewed by the IRBs conform to federal, state and institutional regulations and policies relevant to the health, welfare, safety, rights, and privileges of human subjects; and 2) assist investigators in complying with these regulations and policies.

IRBs constituted in compliance with federal regulations and registered with the federal Office of Human Research Protections (OHRP) have the authority to:

- approve, require modifications to secure approval, and disapprove research protocols and proposed amendments based on consideration of the risks and potential benefits of the research, and whether or not the rights and welfare of human subjects are adequately protected;
- review, accept, or not accept reports, including adverse events, and require modifications to research protocols;
- to require applications for study reapproval from investigators;
- to oversee conduct of the study;
- to suspend or terminate a study; and
- to place irreversible restrictions on a study.

In compliance with 45 CFR 46.112, the institution, its officials, or other institutional committees may not override an IRB decision to disapprove a study.

These policies and procedures apply to all research involving human subjects conducted by UCSD and VASDHS faculty, staff, and students for research conducted completely or partially at UCSD or VASDHS

facilities, or approved off-site locations/facilities, regardless of funding source. These policies and procedures also apply to other institutions or investigators who may enter into agreements with the HRPP to review their human subjects research.

IRBs function independently of, but in coordination with, other committees. The IRB makes its independent determination whether to approve or disapprove a protocol based upon whether or not human subjects are adequately protected.

45 CFR 46 Section 103(a) requires that each institution engaged in Federally-supported human subject research file an “Assurance” of protection for human subjects. The Assurance formalizes the institution’s commitment to protect human subjects. The University of California, San Diego, as part of its Federal Wide Assurance (FWA) numbered FWA00004495 has agreed to protect the welfare of all human subjects involved in research, whether or not the research is conducted or supported by a federal department or agency. Therefore, the UCSD IRB has oversight over all human subject research conducted at these institutions, or by its faculty, students or staff.

The University of California, San Diego has four Institutional Review Boards registered with the federal Office for Human Research Protections that have the authority to review, approve, disapprove, or require changes in research activities involving human subjects. These IRBs have been established in accordance with the requirements of applicable federal rules.

**Applicable
Regulations**

The Belmont Report	21 CFR 56.109(a, f)
38 CFR 16.101	21 CFR 312.34
38 CFR 16.109(a,e)	21 CFR 312.35
38 CFR 16.113	21 CFR 312.80 to 88
45 CFR 46.101	21 CFR 56.112
45 CFR 46.109(a, e)	California Health and Safety Code
45 CFR 46.113	24170-24179.5
21 CFR 50.20	21 CFR 56.113
VHA Handbook 1200.5	

Procedures

Person(s) Responsible	Procedures
UCSD Institutional Official	Authorize and sign Institutional Federalwide Assurance (FWA) Ensure ongoing authority of IRB to perform its function
IRB Administrator	Retain file copy of institutional MPA or FWA and SOPs Conduct administrative review of all new research proposals and on-going studies for completeness. Document discussions of actions in minutes.
IRB Chair (or delegated designee)	Confirm and approve determination that submissions qualify for expedited review

**References
Forms and
Links**

Federalwide Assurance FWA0004495, available from HRPP office

HRPP Program Organization

Policy The UCSD Human Research Protections Program is supported by the Dean’s Office, UCSD School of Medicine and for personnel and fiscal purposes is an administrative unit of the School of Medicine. Support for the program is also provided by the San Diego Veterans Medical Research Foundation (VMRF), and general campus.

The UCSD HRPP has review and oversight responsibility for all research involving human subjects that is conducted by UCSD faculty, staff, or students regardless of the site of performance. Specifically, although the program is administratively located within the School of Medicine, its operations are not limited to School of Medicine researchers and includes UCSD “main campus” faculty in all undergraduate and graduate departments, centers, and programs, as well as VASDHS investigators.

For purposes of Veterans Administration programs, the Institutional Review Boards of the UCSD HRPP function as subcommittees of the VASDHS Research and Development committee. This administrative relationship does not pre-empt or limit the HRPP responsibilities to OHRP, FDA, University of California, and other organizational entities. As noted elsewhere and in accordance with federal regulations, neither the VASDHS R&D committee or any other institutional component may approve research involving human subjects if it has not received approval from a UCSD IRB. Within this document, references to VASDHS research apply to research administered by its associated research foundation, VMRF.

The UCSD HRPP is led by a Director who oversees program operations and also functions as the IRB Administrator of record. The Director reports administratively to the Deputy Vice Chancellor for Health Sciences, and to the UCSD Chancellor for matters involving IRB policy and institutional compliance. There is a Deputy Director and Associate Director who have operational management responsibilities within the program and report to the Director. The Associate Director has personnel management responsibilities for protocol analysts within the HRPP office, and administrative support staff.

Applicable Regulations	38 CFR 16.101 38 CFR 16.109(a,e)	38 CFR 16.113 45 CFR 46.101
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Procedures

Person(s) Responsible	Procedures
IRB Administrator	Program interactions with VASDHS, UCSD Chancellor and Vice Chancellor for Health Sciences Policy and procedure development consistent with federal and local organizational requirements Oversight of program implementation and management
IRB Deputy and Associate Directors	Policy and procedure development in collaboration with IRB Administrator Overall program implementation and management Office personnel management

Review and Updating of SOPPs

Policy This Standard Operating Policy and Procedures (SOPP) document of the Institutional Review Boards must remain current and in compliance with all applicable regulations. To remain current, this SOPP Manual is reviewed and periodically updated. In general, this review will occur at least annually. The periodic review process will update these policies and procedures to comply with the most recent federal, University of California, UCSD, and VA regulations. This review will be documented. Notifications of changes and an updated Policies and Procedures Manual will be distributed to members of IRB committees, HRPP staff as appropriate, and posted on the HRPP website at <http://irb.ucsd.edu>.

Applicable Regulations 38 CFR 16.104 (b) (4) [45 CFR 46.108 \(a\)](#)
[38 CFR 16.108\(a\)](#) [45 CFR 46.115 \(6\)](#)
[38 CFR 16.115 \(6\)](#) [21 CFR 56.108\(a\)](#)
[45 CFR 46.103 \(b\) \(4\)](#) [21 CFR 56.115 \(6\)](#)
[VHA Handbook 1200.5](#)

Procedures	Person(s) Responsible	Procedures
	IRB Chair IRB Administrator	Review these Standard Operating Policies and Procedures at least annually, and at other times as needed, as determined by the Chair or a majority of the IRB members. Document the continuing review and updating. Notify members of changes by summary memo when implemented. Provide updated version of Policies and Procedures Manual to members annually
	HRPP web editor	Create HTML versions of SOPP and update private staff website with revised sections
	IRB Members	Discuss and vote on changes made in continuing review.
	IRB Administrator	Retain file copies of current SOPP Manual and archive copies.

Documentation and Records Retention

Policy The IRB Administrator or his/her designee will prepare and maintain adequate documentation of its activities, including:

1. Copies of all original research proposals reviewed, scientific evaluations, if any, that accompany the proposals, approved consent documents, applications for study reapproval, study progress reports and interim reports, modifications, adverse event report forms submitted by investigators, and other reports submitted to the studies.
2. Minutes of IRB meetings in sufficient detail to show the following:
 - The presence of a quorum throughout the meeting including the presence of one member whose primary concern is in a non-scientific area;
 - Attendance at the meetings including those members who are participating through video or teleconference;
 - Alternate members attending the meeting and members participating by video or teleconference have received and reviewed all required information;
 - The approval of previous meeting minutes;
 - Discussion of expedited reviews and determinations;
 - Actions taken by the IRB;
 - The vote on actions including the number of members voting for, against, and abstaining;
 - That the informed consent document was reviewed in accordance with applicable criteria and contains all of the required elements;
 - The justification for waiving any or all of the required elements of informed consent
 - A determination of risk level of investigational devices;
 - That any IRB member who has a real or potential conflict of interest relative to the proposal under consideration abstained from voting on the proposal (and that the quorum was maintained);
 - The basis for requiring changes in or disapproving research;
 - A written summary of the discussion of controverted issues and their resolution;
 - Review of additional safeguards to protect vulnerable populations if entered as study subjects; and.
 - The frequency of continuing review of each proposal as

determined by the IRB.

3. Copies of all logs, audit reports and continuing review activities, as appropriate.
4. Copies of all correspondence between the IRB and the investigators.
5. A roster of regular and alternate IRB members identified by name; earned degrees; representative capacity; indications of experience such as board certifications, licenses, etc., sufficient to describe each regular and alternate member's chief anticipated contribution to the IRB's deliberations; and any employment or other relationship between each member and the IRB and/or institution (e.g., full-time employee, part-time employee, member of governing panel or board, stockholder, paid or unpaid consultant).
6. Copies of the Standard Operating Policies and Procedures Manual.
7. Statements of significant new findings provided to subjects.
8. Reports of any complaints received by subjects.
9. Access to current conflict of interest statements from IRB members.
10. Training for IRB members and staff.

Consistent with resources available, the UCSD HRPP will attempt to maintain records indefinitely wherever possible. At a minimum, IRB records will be retained for three years after completion of the research at the site or sites over which the IRB has jurisdiction for the study. Records will be retained longer if required by applicable FDA or DHHS regulations or by the sponsor. These records will be accessible for inspection and copying by authorized representatives of the FDA, VA, OHRP, or other appropriate federal departments or agencies at reasonable times and in a reasonable manner.

The Administrator and the administrative staff will securely store and maintain these documents as required to protect the privacy and confidentiality of subjects and sponsor data. All electronic access to these files will be limited to authorized individuals, and access by persons other than IRB, IRB staff, and HRPP officials will be documented, along with the purpose for which the files were accessed, and an audit trail kept of specific projects viewed or copied.

Access to electronic records in computer systems will be limited by appropriate access control measures, and comply at a minimum with Class C2 level security restrictions (i.e., will require individual user ID and password for system access) as defined by Department of Defense Trusted Computer System Evaluation Criteria. Electronic systems will be backed up and have a data recovery and disaster management plan compliant with the DHHS/NIH Automated Systems Security Handbook. User actions with respect to creating, modifying, and deleting data from automated systems will be logged for audit purposes.

Applicable Regulations

21 CFR 56.103(a)	38 CFR 16.103 (b)(4-5)
21 CFR 56.108(a-b)	38 CFR 16.115
45 CFR 46.108 (a)	ICH 3.2.2
45 CFR 46.103 (b)(4-5)	21 CFR 56.115
45 CFR 46.115	VHA Record Control Schedule
38 CFR 16.108 (a)	10-1
	VHA Handbook 1200.5

Procedures

Person(s) Responsible	Procedures
IRB Administrator or designated HRPP staff	<p>Maintain full and complete files for all research studies</p> <p>Maintain roster of regular and alternate IRB members.</p> <p>Establish archive method for files that are not in current use but must still be retained</p> <p>Establish technical and administrative procedures for maintenance of and access to physical and electronic records systems.</p>

References Forms and Links DHHS Automated Information Systems Security Program Handbook (Release 2.0, dated May 1994).

UCSD Institutional Policies

Policy There are a number of local institutional policies that complement federal and state regulations regarding research involving human volunteers. In general UCSD and VASHDS may institute or amend policies as needed that relate to human subjects as long as they do not violate Federal or State regulations, or contravene University of California or Department of Veterans Affairs policy.

Institution-specific policies

1. It is a policy of UCSD that non-salaried faculty may not serve as the Principal Investigator on a study. This policy, however, does not prohibit salaried faculty from submitting an application to the IRB with the non-salaried faculty as a co-investigator.
2. All clinical trials and other human subject activity involving University faculty, staff, and students must be reviewed by UCSD's Institutional Review Board regardless if another IRB has reviewed and/or approved the protocol. Use of an "outside" IRB as a substitute for review by the UCSD IRB is not permissible. The HRPP program recognizes that, on occasion a research sponsor may require use of a common IRB; such practices are permitted only if the outside IRB review and oversight is in addition to that provided by the UCSD HRPP.
3. All clinical trial activity sponsored, in whole or part, by commercial and not-for-profit entities must be negotiated by one of the following offices: UCSD Office of Grants and Contracts, UCSD Central Clinical Trials Office (CTO), or the Veterans Medical Research Foundation.
4. All sponsored clinical trials must have a clinical trial agreement in place, signed by one of the officials authorized to execute UCSD, VASDHS, or VMRF contracts and grants, before initiation of the clinical trial activity. In the case of VASDHS/VMRF trials, they must have VA R&D approval before the trial commences.
5. A copy of all FDA, NIH, Departmental, Divisional, Organizational Research Units, or Center audits and/or letters of warning must be forwarded to the Human Research Protections Program Office, 0052, within two working days after receipt. Failure to comply with this policy may result in suspension of human subjects approval for project(s). Additionally, a copy of all responses to audits and/or letters of warning must be sent to the Human

Research Protection Program Office prior to being sent to the regulatory agencies.

6. As a result of the Moore v. Regents court decision, informed patient consent requires ... that (a) "a physician must disclose personal interest unrelated to the patient's health, whether research or economic, that may affect the physician's professional judgment; and (b) a physicians' failure to disclose such interests may give rise to a cause of action for performing medical procedures without informed consent or breach of confidentiality."
7. General Counsel of the Regents of the University of California has stated that: "If a principal investigator conducts an activity involving human subjects, but does not obtain the approval of the campus Human Subjects Committee, the Regents would not be obligated to defend or indemnify the principal investigator if legal action were instituted by the subject."
8. This institution has policies and procedures for the identification and management of conflict of interest issues of not only IRB members, but of all investigators. These conflicts are reviewed and managed by a separate committee, the Independent Review Committee. When appropriate, conflict of interest information is included in informed consent documents.

Applicable Regulations [California State Supreme Court decision 793 P.2d 479 \(Cal. 1990\) Moore v. Regents of UC](#)

Procedures	Person(s) Responsible	Procedures
	Chair, IRB members and designees	Review research plans and consent documents for compliance with local institutional policy

Section Two: IRB Organization

Composition of IRBs

Policy The IRB consists of at least five regular voting members. Qualified persons from multiple professions and of both genders will be considered for membership. IRB membership will not consist entirely of men, women or of members of one profession. The UCSD HRPP will make every effort to have diverse IRB committees, within the scope of available expertise needed to conduct its functions, and that the IRB possesses appropriate knowledge of the local context in which research for which it is responsible will be conducted. IRB committees may consist of regular and alternate members, and may use the services of special consultants, as required, to provide expertise not available among regular or alternate members.

A. Regular Members

There will be at least one member whose primary concerns are in scientific areas and at least one member whose primary concerns are in nonscientific areas. There will be one member who is not otherwise affiliated with UCSD or VASDHS, and who is not part of the immediate family of a person who is affiliated with either organization. Whenever possible, non-affiliated members will be drawn from the local community, such as clergy, attorneys, representatives of legally recognized veterans organizations, or practicing physicians.

The backgrounds of the regular members will be varied in order to promote complete and adequate reviews of the types of research activities commonly reviewed by the IRB. The regular members will be capable of reviewing research proposals in terms of regulations, applicable law, and standards of professional conduct and practice.

The Director, Deputy Director and Associate Director, Human Research Protections Program will be voting members of one or more IRBs, so that each IRB has a representative of the senior management staff of the HRPP. Wherever practicable, the fraction of members on biomedical IRBs who are VA employees should approximate the fraction of studies that are conducted with VA support or in VA facilities. For the past decade, this has averaged approximately 25% of the overall review and oversight workload of the IRBs. All biomedical IRBs will have at least two VA-salaried (at 5/8ths or more) in accordance with VASDHS policy. At least one of the VA members of the IRB must be present during the review of VA research.

Regular members are expected to make every effort to attend each meeting of IRB, and their presence or absence will be used in establishing a quorum for each meeting. A quorum is composed of a majority of the regular members of the IRB. Performance standards apply to committee participation: each member must, on an annual basis, attend at least eight of 12 monthly meetings, and

One regular member will be designated as the Chair. The Chair will serve as the official representative of the IRB, and will chair all IRB meetings. In the absence of the Chair, the Associate Chair will lead the IRB meeting. In the event that the Associate Chair is unavailable as well, the Chair or Associate Chair will designate another regular IRB member to chair the meeting.

B. Alternate Members

Alternate members are qualified voting members, but they are not expected to attend each meeting. The Chair or his/her designee may ask an alternate member to attend a meeting in order to draw on his/her expertise in an area that may be relevant to that meeting's deliberations and/or to establish a quorum for that meeting. An alternate member's presence at an IRB meeting in the place of an absent regular member may be used in establishing a quorum. Even when not serving as a voting member in place of a regular member, alternate members are encouraged to attend any meeting and they may participate in discussion if they have received applicable meeting materials in advance. An alternate member's absence is not used in establishing a quorum for a meeting.

C. Special Consultants

The Chair or his/her designee may invite individuals with competence in special areas to assist in the review of issues that require expertise beyond or in addition to that available on IRB. These individuals may not vote with the regular and alternate members of the IRB and their presence or absence will not be used in establishing a quorum for an IRB meeting. In some cases it may be necessary to appoint such an individual to the IRB as a full voting member for initial and/or continuing review of a project for which their presence is required, e.g. a prisoner representative for studies involving prisoners.

The decision to engage a consultant will be made by vote at a convened meeting of the IRB. Internal consultants will be identified by a process of communicating the committee's request to the relevant Department

Chair within the institution, or by knowledge of relevant local expertise possessed by IRB committee members or HRPP staff. External consultants will be identified by literature searches to identify nationally-prominent experts in the area under review. Consultants are required to communicate their findings to the IRB in writing. Reasonable compensation will be provided for external consultants, as well as reimbursements for any costs they incur in the course of providing review services.

**Applicable
Regulations**

[21 CFR 56.107 \(a-d, f\)](#)

[21 CFR 56.115 \(a\)\(5\)](#)

[45 CFR 46.107 \(a-d, f\)](#)

[45 CFR 46.115\(a\) \(5\)](#)

[45 CFR 46.103 \(b\) \(3\)](#)

[38 CFR 16.107 \(a-d, f\)](#)

[38 CFR 16.103 \(b\)](#)

[38 CFR 16.115 \(a\)](#)

[ICH3.2.1](#)

[ICH3.2.6](#)

[VHA Handbook 1200.5](#)

Procedures

Person(s) Responsible	Procedures
IRB Administrator and designated staff	<p>Maintain a roster of all regular and alternate members for inspection purposes.</p> <p>Maintain a file on all members, to include their curriculum vita, letters of nomination and other evidence of professional ability.</p> <p>Maintain a roster of available consultants who are eligible and qualified to attend meetings as invited consultants.</p>
IRB Chairs IRB Administrator	<p>Ensure the overall diversity of the IRB membership (gender, race, ethnicity, community affiliation and professional experience) through non-discriminatory selection methods.</p> <p>Ensure that one member representing scientific interests and one member representing non-scientific interests is available for each meeting.</p>

**References
Forms and
Links**

Characteristics of members, including appointment term, committee assignment, departmental affiliation, and professional expertise, are maintained in the HRPP database system, using the Utilities...IRB maintenance functions.

Member Appointment, Compensation and Responsibilities

Policy The UCSD-designated Institutional Official for Human Subjects Protection (i.e., FWA signatory), who is accountable for the Human Research Protections Program, in consultation and approval with the IRB Committee members, and the Director, HRPP, appoints a chair and vice chair of each IRB to serve for renewable two-year terms.

IRB members will be selected in accordance with applicable UCSD and VASDHS policies on committee service. The selection of members and confirmation of alternates will be conducted by the Committee at a convened meeting by majority vote. VA members of the committee will be nominated by the VA R&D committee and appointed by the VASDHS Director.

Members will serve on the IRB for a term of 3 years. Members may be re-appointed for terms based on their concurrence and that of the their department chair and the Institutional Official. The Chair should have at least 1 year of experience as a regular IRB member. IRB chairs and vice-chairs will be elected by a simple majority of the appointed committee members, subject to the approval of the UCSD Institutional Official and VASDHS Director.

A member may resign before the conclusion of his/her term. The vacancy will be filled as quickly as possible. Performance standards apply to committee participation: each regular member is expected to attend at least eight (of 12) monthly meetings per year, and to submit reviews for ten of 12 meetings annually. A member who is not performing his/her responsibilities as expected may be removed by a two-thirds vote of the full membership at a convened meeting. The Chair may also be removed from that position by a two-thirds vote of the full membership at a convened meeting. When unexpected vacancies occur, an alternate member may be selected to fill the vacancy.

The Chair is empowered to temporarily suspend the conduct of human research deemed to place individuals at unacceptable risk pending IRB review. The Chair is also empowered to temporarily suspend the conduct of a study pending IRB review if he/she determines that an investigator is not following the IRB's guidelines. The Chair also may delegate any of his/her responsibilities as appropriate to other qualified and duly appointed members of the IRB.

IRB senior staff, including the program director, deputy director, and associate director, will have training and experience appropriate to their

management responsibilities. Included competencies include a thorough knowledge of applicable federal, state, and university policies relevant to research involving human subjects, and program management experience. IRB Administrative Staff will be clerical and administrative personnel with training, experience, and credentials appropriate for the day-to-day management of the IRB's activities.

The responsibilities of the members of the Board and Staff are summarized as follows:

Position Responsibilities

A. Chairperson:

- Chairs convened meetings.
- Call special meetings when necessary.
- Make decisions in emergency situations to protect subjects and remain in compliance with regulations.
- Confirms primary and secondary reviewer assignments made by HRPP program staff as requested.
- Personally reviews or designates IRB committee member(s) to review SAEs and IND Safety Reports and determines which ones require review by the full board.
- Personally determines or designates IRB committee member(s) to determine whether studies qualify for expedited review (Section 501)
- Performs or delegates review of applications and revisions meeting expedited review criteria.
- Personally reviews or designates IRB committee member(s) to review all submitted investigator reports and determine if there is reason for full IRB review.
- Reviews policies, procedures and forms on an ongoing basis.
- Relates concerns of IRB staff and members to administration regarding issues in human research review.
- Acts as an advisor and educator in the institution's research community.

B. Deputy Chairperson:

- Performs duties of the Chair in his/her absence.
- Assists the Chairperson as needed.

C. IRB Members:

- Review research applications and other appropriate materials prior to convened meetings.
- Provide sufficient advance notice if unable to attend a meeting.

- Attend convened meetings and contribute to Board discussion.
- Review studies according to approval criteria offered in the regulations and SOPPs.
- Serve as primary, secondary reviewer or discussant on selected applications.
- Disclose any potential conflict of interest to the IRB chair as soon as it is recognized.
- Maintain confidentiality regarding any information contained in any review.
- Participate in project audits as needed.
- Review policies, procedures and forms on an annual basis.
- Understand these operating procedures and applicable federal, agency-specific (e.g., VA) and institutional regulations regarding human subjects research.

D. STAFF

HRPP Program Director/IRB Administrator

- Maintains up-to-date knowledge of policies, procedures and regulations regarding human subjects research and IRB operations.
- Represents the Chairman and Board in the institution's community by communicating IRB requirements and decisions with investigators, sponsors, and institutional officials.
- Facilitates the review process with the IRB Chairperson, and members.
- Obtains and distributes information required for chairman or IRB review.
- Assumes additional duties and responsibilities as delegated by the Chairperson.

E. HRPP Administrative Staff

- Maintain up-to-date knowledge of policies, procedures and regulations regarding human subjects research and IRB operations.
- Perform administrative duties to assure systematic flow of work through the IRB.
- Prepare and distribute review materials to members and consultants.
- Maintain files.
- Prepare and distribute minutes.
- Assure accurate and timely documentation, data input, and database up-keep.
- Send out notification of IRB decisions, requests for additional information, and correspondence to investigators in a timely manner.

- Send out timely reminders and notification to investigators when applications for study reapproval are due.

Compensation

Service on the IRB fulfills the University service obligation of UCSD faculty, and organizational service obligation of VA employees. Because of the extensive time commitment required for IRB service, the Vice Chancellor for Health Sciences, UCSD, has approved the following:

- a) For IRB committee chairs, a \$10,000 annual stipend to be paid by HRPP program funds. If the chair is a VA-salaried employee this stipend is contingent upon approval by the VASDHS Director and compliance with applicable VA policies on compensation.
- b) For IRB committee members there is no direct payment, however members whose participation in paperless “e-IRB” reviews requires the use of a computer and high bandwidth network access are eligible to receive a laptop computer, high speed printer, and an annual \$500 Internet connection subsidy to offset costs of DSL or cablemodem service. Members who provide two years of service to the committee are eligible to keep their computer equipment and receive new equipment as replacement.

Applicable Regulations

[45 CFR 46.107\(a\)](#)
[21 CFR 56.107\(a\)](#)

[38 CFR 16.107 \(a\)](#)
[VHA Handbook 1200.5](#)

Procedures

Person(s) Responsible	Procedures
IRB Chair IRB Members	Solicit regular and alternate IRB members from within and outside the institution, and the local community, following an appropriate schedule. Following established criteria, select new members Replace members who resign or leave IRB service.
IRB Administrator	Maintain roster of IRB membership Prepare Dean’s appointment letter and “welcome package” for new members Ensure availability of training materials and educational opportunities for IRB members Create accounting and disbursement infrastructure for compensation to Chairs and committee members.

Orientation and Training

Policy Training of Investigators, IRB members and IRB staff, and research personnel conducting research involving human subjects will meet the requirements set forth in the most recent version of the PHS *Policy on Instruction In The Responsible Conduct Of Research* and any applicable VA guidelines. The IRB will provide training for its members and staff. The institution will provide or recommend a program of instruction for investigators and research staff to comply with this policy and will document its adherence to the provisions of this policy.

A. Training for IRB members:

Prior to attending his/her first IRB meeting as a member, all regular and alternate members will receive, at a minimum, the following:

- 1) UCSD HRPP Standard SOPP Manual
- 2) UCSD IRB Factsheets on selected topics
- 3) FDA Information Sheets and Guidelines when issued
- 4) 45 CFR 46 (PHS/DHHS: Federal Policy for the Protection of Human Subjects)
- 5) The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects
- 6) 21 CFR 50 (FDA: Protection of Human Subjects)
- 7) 21 CFR 56 (FDA: Institutional Review Boards)
- 8) 21 CFR 812 (FDA: Investigational Device Exemptions)
- 9) 21 CFR 312 (Investigational New Drug Application)
- 10) 38 CFR 16 (Protection Of Human Subjects, Common Rule)
- 11) OPRR IRB Guidebook: Protecting Human Subjects
- 12) OPRR Reports and Guidelines
- 13) VHA Handbook 1200.5
- 14) Other materials as appropriate

All IRB members should have completed the UCSD online training modules (at <http://irb.ucsd.edu>) prior to starting as active members, and this should be documented. Prior to attending their first meeting as a voting member, a new committee member should meet with the Chairperson or designee to discuss specific responsibilities and duties and familiarize himself or herself with the committee meeting format. Committee members are also encouraged to attend external meetings where regulatory issues are discussed in order to be knowledgeable about current issues. At the introduction of new/revised SOPP's all IRB members and staff will be provided with a training session on the revised components, normally as part of a scheduled IRB meeting.

B. Training for Investigators and Research Personnel

Investigators and research personnel must comply with all external research training requirements of sponsoring organization (e.g., key personnel training requirements of NIH-funded research). VA investigators will also comply with applicable VA training requirements.

The UCSD HRPP program website contains links to classroom training opportunities and also an online tutorial whose editorial content is maintained by the UCSD HRPP. Additional training may also be required by the IRB in response to noncompliance identified during review or during audits.

The HRPP Office will also provide individuals, upon request, with ready access to copies the Belmont Report and all relevant federal, state, and institutional regulations via its website (<http://irb.ucsd.edu>) and also paper copies on request.

The Human Research Protections Program Office has an ongoing educational program for both IRB members and investigators. Examples of educational opportunities that are offered are as follows:

- 1) Courses through Staff Education and Development. Classes include the application process, informed consent, adverse event reporting, amendment requirements and other processes.
- 2) In-service educational presentations that are regularly scheduled components of convened IRB meetings.
- 3) Classes tailored and presented for specific research units or investigators such as the departments of surgery or psychiatry.
- 4) Annual mandatory educational presentations for VA identified investigators.
- 5) An on-line web tutorial for all investigators and IRB members that meets NIH training guidelines.
- 6) Annual educational programs for undergraduate students.
- 7) Annual educational sessions for Institute of the Americas graduate students.
- 8) Educational sessions for UCSD medical students engaged in research as a component of their Independent Study Project (ISP).
- 9) Educational presentations to new Pharmacy Fellows.

Applicable Regulations

[PHS Policy On Instruction In The Responsible Conduct Of Research 12/01](#)
[38 CFR 16. 107 \(a\)](#)

[45 CFR 46.107 \(a\)](#)
[21 CFR 56.107 \(a\)](#)
[VHA Handbook 1200.5](#)

Procedures

Person(s) Responsible	Procedures
<p>IRB Administrator</p>	<p>Establish new IRB member and staff orientation in:</p> <p><u>Regulations and Guidance</u></p> <ul style="list-style-type: none"> • Drug (21 CFR 312) and Medical Device (21 CFR 812) FDA Regulations • Other FDA Regulations (21 CFR 54) • Protection of Human Subjects (21 CFR 50 and 56, 45 CFR 46, 38 CFR 16 and VHA Handbook 1200.5)) • ICH Guidelines • Other Guidelines (Belmont Report, Declaration of Helsinki, etc.) • Applicable FDA and OHRP guidance documents <p><u>Policies, Procedures and Operations</u></p> <ul style="list-style-type: none"> • Review of Forms (IRB, FDA) • Site Reviews and Reports • Expedited Reviews • Adverse Event Reports • Human Research Advertisements • Scheduling Meetings • Conducting Reviews, including New and Continuing Reviews • Support Staff Responsibilities • Access to Written Resources • Confidentiality Requirements <p><u>Establish new staff training in:</u></p> <ul style="list-style-type: none"> • Use of office computer systems • Management of electronically submitted applications and reviews (“e-IRB”) • Paper files and archiving • Interactions with Sponsors & Investigators • Application for New and Continuing Review • Initial review of project-related correspondence <p>Conduct and document education of new members and staff and periodic continuing education of existing members and staff.</p>

	Maintain access to relevant regulatory and clinical reference materials
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**References
Forms and
Links**

Training links of UCSD HRPP program website: <http://irb.ucsd.edu>

Section Three: IRB Review Procedures

Initial Screening

Policy Applications will be screened by HRPP program staff. Those qualifying for "expedited review" as established by the Secretary, DHHS, (see SOPP on Expedited Review) will be sent to the appropriate IRB Chair (or her/his designee(s)) from among members of the IRB for review.

HRPP protocol analysts will assign a primary and a secondary reviewer from the members of the IRB based on reviewer expertise (and any other relevant consideration, such as individual background and experience) for all protocols requiring full IRB review, working with the IRB Administrator, Deputy or Associate Director. These assignments will be reviewed and approved by the IRB chair or the chair's designee. If the protocol to be reviewed is a commercially-sponsored drug, device or biologic study, the primary and secondary reviewer will receive copies of the sponsor's master protocol, investigator's brochure and the UCSD/VASDHS protocol and consent document(s).

All IRB members will be provided with all available information relevant to initial review. This includes, but is not limited to:

- The research plan
- Consent documents or request for waiver of consent, as permitted by 45 CFR 46.116(d)
- Related grant applications or progress reports available at the time of the IRB application,
- Subject surveys or questionnaires,
- Supporting documentation from sponsors
- Advertisements or other information provided to study participants,
- Drug-related information such as Investigator's Brochures or package inserts.
- Any other information known to be relevant to the scientific merit, determination of safety, risk, and benefit of the study.

This material will be provided to the IRB members so that adequate time is available for a thorough review. In most cases this will be approximately one week prior to the meeting.

Applicable Regulations [45 CFR 46.108](#)

[45 CFR 46.110](#)
[45 CFR 46.116\(d\)](#)

Procedures

Person(s) Responsible	Procedures
IRB Administrator and designated	Perform initial screening of IRB applications for determination whether criteria for expedited review are present.
HRPP program staff	Prepare and distribute documents and meeting agendas for IRB members

Full IRB Review

Policy

During initial review, the IRB reviews new proposals for research involving human subjects submitted by investigators. The purpose of initial review is to ensure protection of the safety, rights and welfare of research participants and compliance with Federal laws and institutional regulations for the protection of human subjects. The IRB has the authority to disapprove, require modifications to secure approval, and approve research protocols based on its consideration of the risks and potential benefits of the research, and whether or not the rights and welfare of human subjects are adequately protected.

At the meeting the IRB, led by the primary reviewer, will: (1) review and discuss the proposal in detail, (2) provide an assessment of the soundness and safety of the protocol, (3) make recommendations for protocol and informed consent revisions and (4) take appropriate action(s) regarding approval. The Principal Investigator may attend the meeting, but only at the invitation of the IRB or the Chair. The Principal Investigator may answer questions or provide additional clarification, but may not be present during deliberations or voting on the proposal.

If a reviewer is absent from the meeting a new reviewer can be designated, as long as the new reviewer has reviewed the requisite materials prior to the meeting, or the secondary reviewer can serve as the primary reviewer. An absent reviewer can submit their written comments to be read at the meeting, as long as another reviewer is present to serve as primary reviewer.

For each protocol, the IRB will determine the frequency of continuing review of the research, designating an interval appropriate to the degree of risk, but not less than once per year from the meeting date. More frequent review may be appropriate if the research is a Phase I or II study or a Significant Risk device study, if it involves vulnerable populations, if the IRB believes that previous studies indicate high incidence of adverse events, or if the IRB believes that close monitoring is indicated. The reasons for such a determination will be included in the minutes.

An approval by the IRB requires that there is not more than one dissenting vote among committee members present. If more than one dissenting vote occurs, the final decision must be deferred or approved pending additional information or modifications that address the concerns of the dissenting members. Only regular members, or in their absence alternate member(s), may vote. A record of the vote will be recorded in the minutes. Any member with a conflict of interest must disclose that conflict of interest

before the project is discussed, and must abstain from voting.

A. Initial Review Process

These guidelines should be followed in the conduct of the initial review of all proposals.

The primary reviewer should lead the discussion by presenting his/her findings and recommendations resulting from the review of the application materials.

Review of the Protocol: The protocol and/or Project Summary will be reviewed by the full IRB to determine if it meets criteria for approval. This includes assessment of risks, benefits, alternatives to participation, determination in the case of clinical trials of which procedures are research vs. standard of care, and other issues as required by applicable human subjects protections regulations and policies. Recommendations for protocol modifications will be made by the reviewers and voted upon. The reviewer may utilize a worksheet such as the Reviewer Checklist to document that each of the specific criteria for approval were discussed and have been met. All worksheets will then be filed in the appropriate study file.

Review of the Investigator and Investigative Site: Members will review the qualifications of the investigator, research staff and investigative site using application materials provided by the investigator. This may include appropriate sections on the initial application form, the investigator's current curriculum vitae, and/or other documents that the IRB may require. For a study involving more than one site, the IRB may decide that the Chair or his/her designee can review those sites.

Review of the Informed Consent Form: The informed consent form will be reviewed by the full IRB to determine if it meets federal and institutional requirements. The IRB may approve consent forms with minor changes at the meeting (e.g.: spelling or grammar changes). The IRB will determine if consent forms requiring major revisions need to be reviewed again by the full IRB prior to approval or can be reviewed by the Chair and/or designee via expedited review. The reviewer may utilize a worksheet such as the Reviewer Checklist for Informed Consent Forms to document the review process.

All translated documents (including informed consent forms, questionnaires, interview guides, and recruitment notices) must be approved by the IRB before they can be used.

Protection of Vulnerable Populations: If the research study proposes to recruit subjects from vulnerable populations, the Committee will review, discuss, and/or require modification to secure approval of the investigator's plan for minimizing undue influence on vulnerable subjects in accordance with applicable federal regulations.

Protection of Confidentiality: The IRB will determine whether there is an appropriate plan to protect the confidentiality of research data that may include coding, removal of identifying information, limiting access to data, use of Certificates of Confidentiality or other methods as appropriate. The IRB will also determine whether methods used to identify and recruit potential participants protect subject privacy and confidentiality and whether the informed consent form adequately discloses the risks to privacy and confidentiality.

Financial Interest Disclosure: The IRB will review the financial disclosure and conflict of interest portions of the Application for Initial Review submitted by the investigator. The Committee will then make a determination as to the presence of conflicts of interest and determine whether changes are needed to the text of the Informed Consent document for the disclosure of same. Note that UCSD and the VA have independent review committees for conflict of interest, and that the findings of these committees, because they may occur after initial IRB approval of a project, may lead to subsequent modifications of research plan and consent or other actions.

Payment to subjects: The IRB will determine whether proposed payments to subjects are appropriate and do not represent an undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject. The method, amount, and schedule of payment should be stated in the consent form, and comply with applicable VA rules for research performed by VA investigators.

Payment for referral of subjects: California law (Health and Safety Code section 445) states that "No person, firm, partnership, association or corporation, or agent or employee thereof, will for profit refer or recommend a person to a physician, hospital, health-related facility, or dispensary for any form of medical care or treatment of any ailment or physical condition." On this basis, cash or cash-equivalent payment to health care providers for referral of subjects or potential subjects is not permitted. Other types of compensation (e.g.: books, other non-cash gifts) must be disclosed and be approved by the IRB prior to implementation.

Review of Advertisements and Recruitment Methods: Members or

designees will review the content of all submitted proposed advertisements, proposed recruitment methods, and all other written material to be provided to subjects. No claims should be made either explicitly or implicitly that the investigational drug or device is safe or effective for the purpose under investigation, or that the drug or device is superior to any other drug or device. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence. In compliance with FDA guidance, advertisements should be *limited* to the following:

- Name and address of the clinical investigator
- Purpose of the research and summary of eligibility criteria
- Straightforward and truthful description of the benefits to the subject
- Location of the research and who to contact for information
- All approved advertisements or ad text will reviewed and stamped by the IRB.

Safety Monitoring: For studies that are blinded, have multiple sites, enter vulnerable populations, or employ high-risk interventions, a general description of the data and safety monitoring plan must be submitted to the IRB as part of the proposed work. This plan must contain procedures for identification and reporting of adverse events. For studies that have a Data Safety Monitoring Board (DSMB), the research plan must make adequate provisions for monitoring the data collected to ensure the safety of subjects.

B. Initial Review of Investigational New Drugs and Chemicals

Drugs and chemicals may be administered to study participants in accordance with applicable FDA and OHRP regulations. Specific review criteria apply for research involving non-approved (“off-label”) uses of approved drugs, use in emergency settings, and use for research purposes of chemicals such as biomarkers and tracers that are not listed in the US Pharmacopeia (USP) or have not been synthesized under FDA Good Manufacturing Practice (GMP) procedures.

When an investigational drug, also referenced as study drug or experimental drug, is used in human research, or a marketed product is used in the context of a clinical research protocol, an approved IND must be on file with the FDA and documented in the application, unless all five of the following conditions are met, as outlined in 21 CFR 312.2:

- (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 21 CFR 312.7.

Other circumstances in which an investigation may be exempt from the requirement for an IND are described in 21 CFR 312.2(b)(2-6).

In studies using pharmaceutical products (particularly when an investigational product is involved), a pharmacist from the UCSD or VASDHS Investigational Drug Service should review the Investigator's Brochure (and VA Form 10-9012 form, if applicable) and communicate any concerns or suggested modifications to the Committee.

C. Initial Review of Investigational Devices

When the research involves an investigational device, the reviewers will assess the investigational device and determine whether it is a significant risk (SR) or a non-significant risk (NSR) device. This assessment will be based on the information provided by the investigator and/or the sponsor and other sources as applicable. The determination of risk will be based on the proposed use of the device and not the device alone. If the device has previously been determined to be a SR device by the sponsor or the FDA, it will be treated as such by the IRB. If the device has previously been determined to be a NSR device by both the sponsor and the FDA, the IRB may agree or disagree with that assessment. The assessment of risk by the IRB will be voted on as part of its review and reported in the minutes.

- 1) Non-significant Risk Devices: when the IRB determines that the device is a non-significant risk device, it proceeds to review the study under requisite criteria for any study. A NSR device investigation does not require the sponsor to first obtain an approved IDE before beginning the study provided certain other requirements are met. If those abbreviated requirements are met, the sponsor is considered to have an approved IDE in place.

- 2) Significant Risk Devices: A device will be determined to be a significant risk device if any of the following criteria apply:
- a) the device is intended as an implant;
 - b) the device supports or sustains human life;
 - c) use of the device is of substantial importance in diagnosing, curing, mitigating, or treating disease, or preventing impairment of health;
 - d) the device could cause significant harm to any subjects;
 - e) subjects must undergo a procedure as part of the device study;
 - f) the study device appears on the FDA list of significant risk devices; or
 - g) the study or any of the study procedures could cause harm to the subjects which:
 - i. could be life threatening,
 - ii. could cause permanent impairment of a body function,
 - iii. could cause permanent damage to body structure, or
 - iv. could necessitate medical or surgical intervention to preclude permanent impairment of a body function or preclude permanent damage to body structure.

Some medical devices are exempted from 21 CFR 812 filing requirements and do not require an approved investigational device exemption (IDE), provided certain conditions are met. However, these kinds of device investigations still require IRB review and informed consent compliance. These are:

- 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.
- A diagnostic device, if the sponsor complies with applicable requirements in Sec. 809.10(c) and if the testing: (1) Is noninvasive, (2) Does not require an invasive sampling procedure that presents significant risk, (3) Does not by design or intention introduce energy into a subject, and (4) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. Note: In

vitro diagnostic (IVD) device research where there is NO possibility of linkage between a sample and subject identification (e.g., surplus blood sample that is coded but the coding cannot be linked to the source subject) does not require Informed Consent compliance.

- 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 device intended solely for veterinary use.
- A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c).
- A custom device as defined in Sec. 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

When the IRB determines that the device is a significant risk device, and an IDE is not provided with the submission, it will notify the investigator and, where appropriate, the sponsor and the FDA. No further action will be taken by the IRB on the research until the sponsor or investigator has filed an IDE application and has met the requirements for a SR study described in 21 CFR 812, or has obtained an equivalent approval (e.g., 510(k) approval) from the FDA and provided documentation of this approval to the IRB.

Humanitarian Device Exemptions will be reviewed in compliance with the provisions of 21 CFR 814.124(a), which establishes the requirement for initial and continuing IRB review.

D. Approval and Documentation

The IRB will vote according to the categories of action described in these SOPPs. The IRB will document in the meeting minutes, and other sources that the criteria for approval of the project and of the informed consent documents have been discussed at the meeting and that the criteria have been met. The results of IRB review and actions taken by the IRB will be communicated to the VA R&D Committee, the investigator, and other institutional officials as appropriate in writing and in a timely manner.

Applicable Regulations

[21 CFR 812.2\(b\)\(1\)\(ii\)](#)
[21 CFR 812.66](#)
[21 CFR 814.124\(a\)](#)
[21 CFR 56.107\(e-f\)](#)
[21 CFR 56.108\(a\)\(1-2\)](#)

[45 CFR 46.111](#)
[38 CFR 16.108 \(a\)](#)
[38 CFR 16.103 \(b\) \(4-5\)](#)
[38 CFR 46.107 \(a, e, f\)](#)
[38 CFR 16.108 \(b\)](#)

[21 CFR 56.108\(c\)](#)
[21 CFR 56.109\(a-f\)](#)
[45 CFR 46.108 \(a\)](#)
[45 CFR 46.103 \(b\) \(4-5\)](#)
[45 CFR 46.107 \(e, f\)](#)
[45 CFR 46.108 \(b\)](#)
[45 CFR 46.109 \(a-e\)](#)

[38 CFR 16.109 \(a-e\)](#)
[38 CFR 16.111](#)
[ICH 3.1](#)
[California Health and Safety Code 445](#)

Links <http://www.fda.gov/cdrh/ode/guidance/1381.pdf> - FDA Humanitarian Device Exemption Review Guidelines

Criteria for Approval of Research Projects

Policy In order to be approved, a project must meet the criteria for approval in this section. This is true of projects reviewed through the full IRB or expedited review, and during both initial approval and annual (or more frequent) continuing reviews.

A. Required criteria:

The following requirements must be satisfied in order for the IRB to approve proposed research (45CFR 46.111):

1. Risks to subjects are minimized by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purpose.
2. Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and in relation to the importance of the knowledge that may be expected to result. In evaluating risks and benefits, the IRB will determine the level of risk of the research, (e.g., minimal, greater than minimal). The IRB will consider only those risks and benefits that may result from the research as distinguished from risks and benefits of therapies that subjects would receive even if not participating in the research. The IRB will not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility.
3. Selection of subjects is equitable. In making this assessment, the IRB

will take into account the purposes of the research, the setting in which the research will be conducted, and the population from which subjects will be recruited. The IRB will be particularly cognizant of the special problems of research involving vulnerable populations, such as children, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons.

4. Informed consent will be sought from each prospective subject or the subject's legally authorized representative, in accordance with, and to the extent required by federal and applicable state and local regulations.
5. Informed consent will be appropriately documented, in accordance with, and to the extent required by federal and applicable state and local regulations.
6. Where appropriate, the research plan makes adequate provision for monitoring the data collected, to ensure the safety of subjects.
7. Where appropriate, there are adequate provisions to protect the privacy of subjects, and to maintain the confidentiality of data.

B. Additional criteria:

The IRB will consider the following additional criteria, when appropriate:

1. Where some or all of the subjects are likely to be vulnerable to coercion or undue influence, such as children, pregnant women, mentally disabled persons, or economically or educationally disadvantaged persons, appropriate additional safeguards have been included in the study to protect the rights and welfare of these subjects.
2. The soundness of research design and the scientific basis for the proposed research. The IRB will review the design and scientific basis to the extent that it relates to the risks to subjects and the benefits of the study, including the generalized knowledge to be gained.
3. The selection of subjects should reflect the purposes of the research and the group that will benefit from the research outcome. The IRB will place special emphasis on the inclusion of minorities and both genders in study populations so that research findings can be applied to all persons at risk for the disease, disorder or condition under study. The proposed research should specify the gender and racial/ethnic composition of the subject population, if it differs from that of the general population, as well as justification for inclusion or exclusion of

any subpopulation.

4. Where some or all of the subjects are likely to have reduced decision-making capacity or require surrogate consent, appropriate additional safeguards have been included in the study and the review process to protect the rights and welfare of these subjects.
5. The IRB will also consider the following criteria during initial review, as appropriate to the type of study being proposed:
 - Whether the purpose of study is clear
 - Results of any related studies
 - The number of subjects and duration of participation is stated and appropriate
 - Duration of the study and frequency of activities are clear and appropriate
 - Wash-out period for medications is appropriate and safeguards are in place to assure subject's condition will be adequately monitored during that period
 - Use of placebo is appropriate
 - The setting in which research occurs is appropriate.
 - Plan for recruiting subjects including recruitment and enrollment procedures and appropriateness of claims made in advertising.
 - The nature or amount of the compensation offered to subjects for participation in research does not create undue influence, particularly for economically disadvantaged subjects.
 - The risks of research activities are clearly distinguished from the risk of relevant standard healthcare.
 - Physical, psychological, social and economic risks, including risks to privacy and the probability of occurrence posed by research design, interventions and procedures.
 - When reviewing a research proposal with elements warranting special attention (e.g., placebos, challenge studies, radiation exposure, deviations from standards of care), the IRB will consider the appropriateness of, and rationale for, such elements and document such considerations.
 - Attestation, when required, by the investigator as to whether the proposal, or one substantially similar to it, has been disapproved by another IRB.
 - Process for monitoring and reporting adverse events.
 - Presence of a Data Safety Monitoring Board (DSMB) if applicable.
 - Information to be used for recruitment or to inform subjects or potential subjects about the nature of the research.
 - The investigator and research staff have appropriate scientific and human subject protection training to conduct the study.

- Investigator potential financial conflicts.

Applicable Regulations [21 CFR 812.2\(b\)\(1\)\(ii\)](#) [38 CFR 16.103 \(b\) \(4-5\)](#)
 [21 CFR 812.66](#) [38 CFR 16.111](#)
 [21 CFR 56.108\(a\)\(1-2\)](#) [ICH 3.1](#)
 [45 CFR 46.109 \(a-e\)](#)
 [45 CFR 46.111](#)

Procedures	Person(s) Responsible	Procedures
	Reviewer(s)	Assess risks, benefits and the adequacy of subject protections Determine whether approval criteria have been met Make recommendations as to IRB action Submit written review comments
	IRB Members	Discuss project in light of approval criteria and vote on approval
	IRB Administrator	Document in minutes that approval criteria have been met, maintain reviewer written comments

Informed Consent

Policy No investigator may involve a human being as a subject unless legally effective informed consent has been obtained from the subject or the subject's authorized representative, or if the conditions for waiver of consent have been met. Consent will be sought only under circumstances that provide the prospective subject or the representative sufficient opportunity to consider whether or not to participate and that minimize the possibility of coercion or undue influence. The information should be provided in language that is understandable to the subject or representative. The informed consent, whether oral or written, will not contain any exculpatory language through which the subject or representative is made to waive or appear to waive any of the subject's legal rights, or releases or appears to release the investigator, the institution, the sponsor or its agents from liability for negligence.

A. Documentation of Written Informed Consent

The IRB requires documentation of informed consent by use of a written consent form approved by the IRB that is signed and dated by the subject or the subject's authorized representative. Investigators will use informed consent documents that are appropriate to the institution that is administering the project and the site of participant recruitment. Consent forms will vary somewhat in format and in language describing compensation for research injury due to administrative requirements of the University of California, VASDHS, the Veterans Medical Research Foundation, and San Diego Children's Hospital. However, all consent forms must contain the elements required by federal regulations and no participant should sign more than one equivalent consent. VA-funded investigators will use VA Form 10-1086 or other VA-approved formats to document informed consent. If someone other than the investigator conducts the interview and obtains consent from a patient, the investigator needs to formally delegate this responsibility, and the person so delegated must have received appropriate training to perform this activity. The person so delegated must be knowledgeable about the research to be conducted and the consenting process, and must be able to answer questions about the study. The person explaining the study to the subject, if other than the investigator, must also sign the informed consent form on the appropriate line. A copy of the informed consent form will be given to the person signing the form, and the original placed in the archival research record maintained by the PI.

Please note for VASDHS clinical research a copy of the consent form must be placed in the patient's VA medical record.

The consent form may be either of the following:

- A written consent document that embodies the elements of informed consent described in 21 CFR 50.25. This form may be read to the subject or the subject's authorized representative, but, in any event, the investigator will give either the subject or the representative adequate opportunity to read it before it is signed.
- A "short form" written consent document stating that the elements of informed consent as required above have been presented orally to the subject or the subject's authorized representative. When this method is used, there will be an impartial witness to the oral presentation. The IRB will approve the written summary of what is to be said to the subject or representative. Only the short form itself is to be signed by the subject or the representative. However, the witness will sign both the short form and a copy of the summary, and the person actually obtaining the consent will sign a copy of the summary. A copy of the summary will be given to the subject or the representative in addition to a copy of the short form.

For clinical studies it is recommended as a best practice that a progress note documenting the informed consent process be placed in the subject's medical record and signed by the investigator. At a minimum, the progress note should include the name of the study, the person consenting the subject, a statement that the study was explained to the subject or the subject's representative, a statement that the subject was given the opportunity to ask questions, and documentation that consent was obtained before any subject procedures were performed.

The informed consent form will have signature lines for the subject, a witness to the signing of the consent, and optionally, the signature of the person administering the consent. VA consent forms will contain lines for signature consistent with the VA 10-1086 format.

A signature line for the subject's authorized representative may be included if the project meets California requirements for Surrogate Consent and the project has been approved for use of Surrogate Consent by the IRB. See the section on Research involving persons with impaired decisional capacity for additional information on this topic.

The research subject will be given a signed copy of the consent form, and a copy of the Experimental Subjects Bill of Rights.

B. Required Elements of Informed Consent Forms

In accordance with 21 CFR 50.25, 38 CFR 16.116, 45 CFR 46.116 and VHA Handbook 1200.5, the following information will be provided to each subject:

1. A statement that the study involves research, an explanation of the purposes of the research, the expected duration of the subject's participation, a description of the procedures to be followed, and identification of any procedures which are experimental.
2. A description of any reasonably foreseeable tangible or intangible risks or discomforts to the subject.
3. A description of any benefits to the subject or to others that may reasonably be expected from the research.
4. A disclosure of appropriate alternative procedures or courses of treatment, if any, which might be advantageous to the subject.
5. A statement describing the extent, if any, to which confidentiality of records identifying the subject will be maintained.
6. For research involving more than minimal risk, an explanation as to whether any compensation, or medical treatments are available, if injury occurs and, if so, what they consist of, or where further information may be obtained.
7. An explanation of whom to contact for answers to pertinent questions about the research and research subjects' rights, and whom to contact in the event of a research-related injury to the subject.
8. A statement that participation is voluntary, that refusal to participate will involve no penalty or loss of benefits to which the subject is otherwise entitled, and that the subject may discontinue participation at any time without penalty or loss of benefits to which the subject is otherwise entitled.
9. A statement regarding care that will be provided in the event of a research-related injury. For sponsored studies, a statement naming the organization that will pay for injury costs should be included. For VA projects, information on VA procedures related to research subject injury will be included.

10. If the research involves products regulated by the FDA or will be used to support applications for products regulated by the Food and Drug Administration (a drug with an IND or a medical device with an IDE), the consent form will include a statement disclosing that the FDA (Food and Drug Administration) may choose to inspect research records identifying study participants.

All informed consent forms should be written at a level appropriate for the potential population. Use of the second person is preferred. General formatting, readability and clarity must be acceptable and medical terminology must be defined in lay terms, ideally at an 8th grade reading level or lower.

C. Additional Elements Of Informed Consent

When appropriate, one or more of the following elements of information will also be provided to each subject:

1. A statement that the particular treatment or procedure may involve risks to the subject (or to the embryo or fetus if the subject is or may become pregnant) that are currently unforeseeable.
2. Anticipated circumstances under which the subject's participation may be terminated by the investigator.
3. Any additional costs to the subject that may result from participation in the research, with consideration of Federal laws concerning veterans' eligibility for medical care and treatment.
4. The consequences of a subject's decision to withdraw from the research and procedures for orderly termination of participation by the subject.
5. A statement that significant new findings developed during the course of the research which may relate to the subject's willingness to continue participation will be provided to the subject.
6. The approximate number of subjects involved in the study.
7. Additional information pertaining to the use of biological materials for research, especially genetic research.
8. The amount of payment, if any, the subject is to receive, and the schedule of payment. This amount must be pro-rated over the length of the study.

9. A description of any financial or other arrangements with a sponsor or institution that may pose a conflict of interest.
10. Any additional information that may be required by state, federal, or institutional regulations in order for informed consent to be legally effective.
11. Additional information that, in the judgment of the IRB, would add meaningfully to the protection of the rights, safety, and/or well being of the subjects.
12. For VASDHS research, additional requirements for consent wording may apply. For example, some veterans are required to pay co-payments for medical care and services provided by VA. These co-payments continue to apply to medical care and services provided by the VA that are not part of a research study.

D. Waiver or Alteration of Informed Consent

For studies involving products regulated by the FDA under an IND or IDE, waiver of written informed consent is not permitted. For other studies, the IRB may approve a consent procedure that alters some or all of the elements of informed consent set forth in this section, consistent with the provisions of the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Although HIPAA addresses waiver of authorization (consent) in settings using information derived from healthcare settings, for consistency the provisions of HIPAA will be applied by the IRB to all research involving person-identifiable information.

The HIPAA Privacy Rule 45 CFR 164 section 512(I) requires that requires that eight conditions must be satisfied in order to grant a waiver of individual authorization for research uses of Protected Health Information (PHI , i.e., person-identifiable information produced as a result of healthcare services). In addition to these criteria, the federal Common Rule (45 CFR 46 section 116(d)) stipulates that “whenever appropriate, the subjects will be provided with additional pertinent information after participation.”

The IRB may waive the requirements to obtain informed consent provided the IRB finds and documents that all of the following conditions apply:

- The research involves no more than minimal risk
- Granting of waiver will not adversely affect privacy rights and

welfare of the individuals whose records will be used.

- The project could not practicably be conducted without a waiver
- The project could not practicably be conducted without use of PHI
- The privacy risks are reasonable relative to the anticipated benefits of research
- An adequate plan to protect identifiers from improper use and disclosure is included in the research proposal
- An adequate plan to destroy the identifiers at the earliest opportunity, or justification for retaining identifiers, is included in the research proposal
- The project plan includes written assurances that PHI will not be re-used or disclosed for other purposes.
- Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

The IRB may also waive the requirement for the investigator to obtain a signed consent form for some or all subjects, if it finds either:

- the only record linking the subject and the research would be the consent document, and the principal risk would be potential harm resulting from a breach of confidentiality; or ,
- that the research presents no more than minimal risk of harm to subjects, and involves no procedures, for which written consent is normally required outside of the research context.

In cases where the written informed consent is waived, the IRB may require the investigator to provide subjects with a written statement containing information about the research and appropriate elements of informed consent. The IRB will document in the minutes its specific findings that conditions permitting waiver or alteration have been met.

The informed consent requirements in this policy are not intended to preempt any applicable Federal, State, or local laws which require additional information to be disclosed in order for informed consent to be legally effective.

E. Obtaining Consent From Those Who Cannot Read Or Speak English Or Who Are Illiterate

Individuals unable to speak English may not be excluded from participating in a study. The subject must be given an approved translation of the consent form and the Experimental Subject's Bill of Rights in their native language to sign. Unless the researchers are fluent in

the subject’s language, a qualified translator must be included in the consent process and then sign his or her name at the end of the approved translated consent form. A relative who speaks English does not usually qualify as an official translator unless the person has some training in medical terminology or has a medical background.

If an investigator wishes to include a subject who is illiterate or cannot read the informed consent document the consent form will be read to the subject in the presence of an impartial witness. Whenever possible, accommodations should be made to permit subjects to read the consent form if possible (e.g., large type for individuals with visual impairments), rather than relying on verbal consent routinely. The information presented to the subject must include all of the required elements of consent and should be at least as extensive as found in the written consent form. An impartial witness will observe and/or take part in the consent process and then sign the consent form. The person who is illiterate will also sign their mark on the signature line. When a study is expected to include illiterate subjects, the investigator will describe during initial review how the consent process is to be carried out and will submit a “short form” for approval.

Applicable Regulations

[21 CFR 50.20](#)
[21 CFR 50.23\(a-d\)](#)
[21 CFR 50.25](#)
[21 CFR 50.27](#)
[21 CFR 56.104\(c\)](#)
[45 CFR 46.116, 117](#)

[38 CFR 16.116, 117](#)
[45 CFR 46.117\(a,c\)](#)
[45 CFR 46.116\(c, d\)](#)
[VHA Handbook 1200.5](#)
[OHRP Guidance](#)
[California law AB2328](#)

Procedures

Person(s) Responsible	Procedures
IRB Members	<p>Review informed consent forms for compliance with applicable federal, state and institutional regulations and policies.</p> <p>Assess reading level and general readability of the form.</p> <p>Make recommendations on the adequacy of the form for its intended purpose and require changes if necessary.</p>

Emergency Use and Informed Consent

Policy A. Emergency Exemption from Prospective IRB Approval

1. Emergency Use

Emergency use of an investigational product may be permitted in a human subject outside of an approved study without prior IRB approval if the situation is life-threatening, there is no standard acceptable treatment, and there is not sufficient time to obtain IRB approval. Prior to administering the test article, the investigator must notify the IRB Chair and the UCSD HRPP office. Use under this mechanism does not constitute IRB approval. Following emergency use of the test article outside of an approved study, the investigator must submit relevant documentation to the IRB for review within 5 working days, certifying that:

- The human subject was confronted by a life-threatening situation necessitating the use of the test article.
- There was no alternative method of approved or generally recognized therapy available that provided an equal or greater likelihood of saving the life of the subject.

Planned use of a test drug or device in an emergency setting will be permitted if the study procedures comply with applicable OHRP and FDA guidance on planned emergency research. Planned emergency research by SDVAHS investigators will comply with relevant VA policy on research in emergency settings.

2. Exception from Informed Consent

Even for emergency use, the investigator is required to obtain informed consent from the subject or the subject's legally authorized representative if possible. If informed consent can not be obtained, the investigator and a physician not otherwise participating in the human subjects research must adequately certify the following in writing prior to use of the test article:

- The human subject was confronted by a life-threatening situation necessitating the use of the test article.
- Informed consent could not be obtained from the subject because of an inability to communicate with, or obtain legally effective consent from, the subject
- Time was not sufficient to obtain consent from the subject's legal

representative

- There was no alternative method of approved or generally recognized therapy available that provided an equal or greater likelihood of saving the life of the subject.

If immediate use of the test article is, in the investigator's opinion, required to preserve the life of the subject, and time is not sufficient to obtain an independent physician's opinion prior to administering the test article, the determinations of the investigator must be reviewed in writing within 5 working days after the use of the test article by a physician not otherwise participating in the human subjects research. In this event, a copy of the independent review must be submitted to the IRB within 7 working days after the use of the test article.

The IRB will review the submitted documents and will indicate the regulatory basis for the emergency use and that its use was appropriate. Data obtained from such emergency use may not be published or otherwise used for research purposes. Submission of a research proposal by the investigator is required if future use of the test article is anticipated.

3. Exemption from Informed Consent Requirements for Planned Emergency Research

The IRB may approve proposals for emergency research without requiring that informed consent of all research subjects be obtained if it finds and documents (with the concurrence of a licensed physician who is a member of or consultant to the IRB and who is not otherwise participating in the clinical investigation) all of the following:

- a) The human subjects are in a life-threatening situation, available treatments are unproven or unsatisfactory, and the collection of valid scientific evidence, which may include evidence obtained through randomized placebo-controlled investigations, is necessary to determine the safety and effectiveness of particular interventions.
- b) Obtaining informed consent is not feasible because:
 - The subjects will not be able to give their informed consent as a result of their medical condition;
 - The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
 - There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in

the human subjects research.

- c) Participation in the research holds out the prospect of direct benefit to the subjects because:
- subjects are facing a life-threatening situation that necessitates intervention;
 - Appropriate animal and other preclinical studies have been conducted, and the information derived from those studies and related evidence support the potential for the intervention to provide a direct benefit to the individual subjects; and
 - Risks associated with the investigation are reasonable in relation to what is known about the medical condition of the potential class of subjects, the risks and benefits of standard therapy, if any, and what is known about the risks and benefits of the proposed intervention or activity.
- d) The human subjects research could not practicably be carried out without the waiver.
- e) The proposed investigational plan:
- Defines the length of the potential therapeutic window based on scientific evidence, and,
 - The investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and;
 - If feasible, the investigator has committed to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent
 - The investigator will summarize efforts made to contact legally authorized representatives and make this information available to the IRB at the time of continuing review.
- f) The IRB has reviewed and approved informed consent procedures and an informed consent document. These procedures and the informed consent document are to be used with subjects or their legally authorized representatives in situations where use of such procedures and documents is feasible.
- g) Additional protections of the rights and welfare of the subjects

will be provided, including, at least:

- (i) Consultation (including, where appropriate, consultation carried out by the IRB) with representatives of the communities in which the human subjects research will be conducted and from which the subjects will be drawn;
- (ii) Public disclosure to the communities in which the human subjects research will be conducted and from which the subjects will be drawn, prior to initiation of the human subjects research, of plans for the investigation and its risks and expected benefits;
- (iii) Public disclosure of sufficient information following completion of the human subjects research to apprise the community and researchers of the study, including the demographic characteristics of the research population, and its results;
- (iv) Establishment of an independent data monitoring committee to exercise oversight of the human subjects research; and
- (v) If obtaining informed consent is not feasible and a legally authorized representative is not reasonably available, the investigator has committed, if feasible, to attempting to contact within the therapeutic window the subject's family member who is not a legally authorized representative, and asking whether he or she objects to the subject's participation in the human subjects research. The investigator will summarize efforts made to contact family members and make this information available to the IRB at the time of continuing review.

The study plan must ensure that, at the earliest feasible opportunity, each subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, is informed of the subject's inclusion in the human subjects research, the details of the investigation and other information contained in the informed consent document.

The study plan must also ensure that there is a procedure to inform the subject, or if the subject remains incapacitated, a legally authorized representative of the subject, or if such a representative is not reasonably available, a family member, that he or she may discontinue the subject's participation at any time without penalty or loss of benefits to which the subject is otherwise entitled. If a legally authorized representative or family member is told about the human subjects research and the subject's condition improves, the subject is

also to be informed as soon as feasible.

If a subject is entered into human subjects research with waived consent and the subject dies before a legally authorized representative or family member can be contacted, information about the human subjects research is to be provided to the subject's legally authorized representative or family member, if feasible.

If the study involves any FDA regulated product and involves an exception to informed consent, there must be a separate IND or IDE for the study.

If the IRB approves the exemption, its evaluation and the regulatory basis for approving the exemption will be documented. If the IRB determines that it cannot approve human subjects research because the investigation does not meet the criteria for exemption in part B of this section or because of other relevant ethical concerns, the IRB will document its findings and provide these findings promptly in writing to the clinical investigator and to the sponsor of the human subjects research .

Applicable Regulations

[21 CFR 56.104\(c\)](#)
[45 CFR 45.116](#)

[21 CFR 50.20](#)
[21 CFR 50.23\(a-d\)](#)
[21 CFR 50.24](#)
[VHA Handbook 1200.5](#)

Procedures

Person(s) Responsible	Procedures
IRB Chair	Review the Emergency Use documentation provided by the investigator in a timely manner Decide whether an emergency conference call of the IRB is indicated to discuss the matter
IRB Administrator	Maintain telephone contact with investigator to quickly secure necessary documentation. Schedule emergency use review meeting by conference call or in person in a timely manner. Provide investigator with relevant correspondence in a timely manner.

Confidentiality and De-Identification of Research Records

Policy

A guiding principle of research involving human volunteers is that a participant's privacy must be respected and confidentiality of person-identifiable data must be preserved.

The IRB will determine whether there is an appropriate plan to protect the confidentiality of research data that may include coding, removal of identifying information, limiting access to data, use of Certificates of Confidentiality or other effective methods. The IRB will also determine whether methods used to identify and recruit potential participants protect subject privacy and confidentiality and whether the informed consent form adequately discloses the risks to privacy and confidentiality. Physical safeguards for research data will also be reviewed by the IRB, such as maintenance of records in locked files, separation of person-identifiable demographics data from study data referenced only to a unique study ID, etc.

Access to research data should be based on a "need to know" and "minimum necessary" standard. Investigators should use and communicate person-identifiable information about research participants only when it is essential to the scientific goals of a research study.

As a general policy, the criteria used by the IRB for judging the safeguards for participant confidentiality will be those of the Privacy Rule of the Health Insurance Portability and Accountability Act of 1996 (HIPAA). Although HIPAA addresses only a specifically defined set of information called Protected Health Information (PHI) derived from healthcare service events, its principles represent a best practice for all person-identifiable research data.

In the informed consent procedure, subjects are often given assurances that the confidentiality of records identifying the subjects will be maintained. Loss of confidentiality may occur however when a court orders that research files or information be submitted as evidence in a legal matter. The court decides who has access to the files and what information may be required to be provided.

Unless there is no person-identifiable information kept in research records, complete confidentiality of records identifying the subjects may be assured only to the extent that disclosure is not compelled by court order. When FDA regulated products are being studied, the informed consent document should state that the FDA may review and copy the subject's medical

records and, if necessary, obtain the identity of the subject.

Certificates of Confidentiality

Persons engaged in biomedical, behavioral, clinical, or other research (including research on mental health, the use and effect of alcohol and other psychoactive drugs) to protect the privacy of individuals who are the subject of such research by withholding from all persons not connected with the conduct of such research the names or other identifying characteristics of such individuals. Persons so authorized to protect the privacy of such individuals may not be compelled in any Federal, State or local civil, criminal, administrative, legislative, or other proceedings to identify such individuals. (Public Health Service Act, S 301(d), 42 U.S.C. s 241 (d), as added by Pub. L. No. 100-607, S 163 (November 4, 1988)).

A Certificate of Confidentiality is granted when the research is of a sensitive nature where the protection is judged necessary to achieve the research objectives. Research can be considered sensitive if it involves the collection of information in any of the following categories:

- (a) Information relating to sexual attitudes, preferences, or practices;
- (b) Information relating to the use of alcohol, drugs, or other addictive products.
- (c) Information pertaining to illegal conduct;
- (d) Information that if released could reasonably be damaging to an individuals' financial standing, employability, or reputation within the community;
- (e) Information that would normally be recorded in a patient's medical record and the disclosure of which could reasonably lead to social stigmatization or discrimination;
- (f) Information pertaining to an individual's psychological well being or mental health.

See the Procedures section for further information on Certificates of Confidentiality

Data De-identification

HIPAA contains in Section 164.514 a “safe harbor” provision that states information may be considered “de-identified” ie., anonymous if it does not contain any of the following elements:

1. Names;
2. All geographic subdivisions smaller than a State, including street

address, city, county, precinct, zip code, and their equivalent geocodes, except for the initial three digits of a zip code if, according to the current publicly available data from the Bureau of the Census: (1) The geographic unit formed by combining all zip codes with the same three initial digits contains more than 20,000 people; and (2) The initial three digits of a zip code for all such geographic units containing 20,000 or fewer people is changed to 000.

3. All elements of dates (except year) for dates directly related to an individual, including birth date, admission date, discharge date, date of death; and all ages over 89 and all elements of dates (including year) indicative of such age, except that such ages and elements may be aggregated into a single category of age 90 or older;
4. Telephone numbers;
5. Fax numbers;
6. Electronic mail addresses;
7. Social security numbers;
8. Medical record numbers;
9. Health plan beneficiary numbers;
10. Account numbers;
11. Certificate/license numbers;
12. Vehicle identifiers and serial numbers, including license plate numbers
13. Device identifiers and serial numbers;
14. Web Universal Resource Locators (URLs)
15. Internet Protocol (IP) address numbers;
16. Biometric identifiers, including finger and voice prints;
17. Full face photographic images and any comparable images; and
18. Any other unique identifying number, characteristic or code

The Privacy Rule requires in addition that a researcher “does not have actual knowledge that the information could be used alone or in combination with other information to identify an individual who is the subject of the information.” In other words, even if the 18 elements are removed, if a researcher knows there is a way using the remaining information to re-identify an individual uniquely, then the information is not considered de-identified.

As a policy the IRB will use HIPAA criteria for de-identification of research data.

Applicable Regulations [Privacy Rule of the Health Insurance Portability and Accountability Act of 1996, section 164.514](#)

Procedures

Person(s) Responsible	Procedures
IRB members	Review recruitment and data management plans for research projects for compliance with confidentiality protections.
Principal Investigators	Certificates of Confidentiality can be obtained by writing to: Office of Research Management National Institutes of Mental Health 6100 Executive Blvd., Room 8102 Mail Stop: MSC 9653 Bethesda, Maryland 20892-9653 Telephone: (301) 443-2578 Website for Certification Information: http://www.nimh.nih.gov/research/confident.cfm

**References
Forms and
Links**

HIPAA Privacy rule text: <http://aspe.hhs.gov/admsimp/bannerps.htm>

For an overview of the impact of HIPAA on biomedical research, see:
<http://www.hhs.gov/ocr/hipaa/research.html>

Review of Projects Involving Protected Populations

Policy

In studies where subjects likely to be vulnerable to coercion or undue influence are likely to participate, appropriate additional safeguards must be included in the study to protect their rights and welfare. In such cases, the investigator must provide sufficient justification for inclusion of vulnerable populations and a plan for how the rights of these subjects will be protected from possible coercion. The IRB must determine whether the involvement of such populations in research is justified and determine whether the proposed study minimizes or eliminates the risks to vulnerable subjects.

In making such determinations the IRB will consider the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits (eg: the likelihood of benefit to the subject). The IRB will also determine whether relevant risks and benefits are thoroughly presented in documents and procedures used in the informed consent process. Issues that should be addressed by the IRB include whether:

- any monetary payments to subjects are not so great as to constitute an undue inducement;
- the proposed safeguards are adequate to protect the rights and welfare of the subjects;
- minorities receive an equal share of the benefits of research and do not bear a disproportionate burden;
- the possibility of exploitation can be reduced or eliminated.

Policy and procedure for prisoners, students and employees is provided here. Because of the complexity of the issues, specific policy guidance is provided in separate sections of this Policy and Procedures document for the following vulnerable populations: a) pregnant women and fetuses, b) children and c) research participants with impaired decision making capacity, and those likely to need surrogate consent.

A. Prisoners as a vulnerable population in research

If an investigator indicates on the Initial Application Form that prisoners may participate in the research, the following additional requirements will apply to IRB review of the project.

The IRB reviewing human research involving prisoners must meet the following specific requirements:

1. At least one member of the IRB will be a prisoner, or a prisoner

representative with appropriate background and experience to serve in that capacity, except that where a particular research project is reviewed by more than one IRB, only one IRB need satisfy this requirement.

2. A majority of the IRB (exclusive of prisoner members) will have no association with the prison(s) involved, apart from their membership on the IRB.
3. The research goals of the project include one or more of the following:
 - a) Study of possible causes, effects, and processes of incarceration, and of criminal behavior, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - b) Study of prisons as institutional structures or of prisoners as incarcerated persons, provided that the study presents no more than minimal risk and no more than inconvenience to the subjects;
 - c) Research on conditions particularly affecting prisoners as a class (for example, vaccine trials and other research on hepatitis which is more prevalent in prisons than elsewhere; and research on social and psychological problems such as alcoholism, drug addiction, and sexual assaults) provided that the study may proceed only after the IRB has consulted with appropriate experts including experts in penology, medicine and ethics, and published notice in the Federal Register, of his intent to approve such research; or
 - d) research on practices, both innovative and accepted, that have the intent and reasonable probability of improving the health or well being of the subject. In cases where those studies require the assignment of prisoners in a manner consistent with protocols approved by the IRB to control groups, which may not benefit from the research, the study may proceed only after the UCSD HRPP has consulted with appropriate experts, including experts in penology, medicine and ethics, and published notice in the Federal Register, of his intent to approve such research.
4. Any possible advantages accruing to the prisoner through participation the research, when compared to the general living conditions, medical care, quality of food, amenities, and opportunity for earnings in prison, are not of such a magnitude that the prisoner's ability to weigh the risks and benefits of the research in the limited-choice environment of the prison is impaired.

5. The risks involved in the research are commensurate with risks that would be accepted by non-prison volunteers.
6. Procedures for the selection of subjects within the prison are fair to all prisoners and immune from arbitrary intervention by prison authorities or prisoners. Unless the principal investigator provides the IRB justification in writing for following some other procedures, control subjects must be selected randomly from the group of available prisoners who meet the characteristics needed for that particular research project;
7. Any information given to subjects is presented in language that is appropriate for the subject population.
8. Adequate assurance exists that parole board(s) will not take into account a prisoner's participation in the research in making decisions regarding parole, and each prisoner is clearly informed in advance that participation in the human subjects research will have no effect on his/her parole.
9. Where there is need for follow-up examination or care of participants after the end of their participation in the research, adequate provision has been made for such examination or care, taking into account the varying lengths of prisoner sentences, and for informing participants of this fact.
10. In cases involving VA research, the UCSD HRPP will certify to the VA Chief Research and Development Officer (CRADO) that the review of research involving prisoners as research subjects has been conducted in accordance with these requirements. The research may not be conducted without the approval of the CRADO.

In addition to meeting Federal regulations, the project must comply with all state and local requirements for inclusion of prisoners as subjects.

These policies also apply to subjects enrolled in a study who become incarcerated during the course of the study and remain incarcerated at the time that study-related procedures or treatment are to be performed. In order for study procedures to be performed while the subject is incarcerated, the study and its review must have met all of the requirements above. Incarceration will thus usually result in suspension or discontinuation from the study, depending on the circumstances of protocol and the duration of the incarceration. Subjects discontinued from a study due to incarceration must be withdrawn in an orderly manner that

assures their safety. Their participation in the study may resume after release if the protocol allows.

Studies involving a subject population with a high probability of becoming incarcerated during the study (e.g., violent felons) may also be required to meet these requirements. The IRB will review such studies on a case-by-case basis. If the IRB determines that prisoner requirements will be applied, then the project and review process must meet the above criteria or be disapproved.

B. Students and Employees

Students (undergraduate, graduate, and medical students), and employees of UCSD, SDVAHS, and SDCHS (administrative, clerical, nursing, lab technicians, post-doctoral fellows and house staff, etc.) are considered vulnerable to undue influence. Such individuals may feel some pressure to participate in a researcher's study, especially if the requesting researcher is their supervisor, instructor, or someone who might be in a position to influence their future. Investigators must exercise great caution to avoid even the appearance of pressuring such individuals into enrollment or continued participation. When a UCSD or VASDHS research investigator wishes to include such individuals as human subjects, he or she must indicate so on the initial application or request a modification to an approved protocol.

In general, the IRB does not permit recruitment of employees from the investigator's own lab, department, or office, as a matter of local policy. However, for minimal risk studies the IRB will consider requests for waivers of this policy on a case-by-case basis. Students from an investigator's own lab or class may not be actively recruited into their research studies, but such students may freely volunteer to participate, to the same extent as anyone is free to respond to general recruitment advertisements.

When students participate in research studies for class credit they should be provided alternative methods of getting that credit that do not include participating in an experiment, and it is the investigator's responsibility to determine that those alternative methods exist. Wherever possible, student should be provided with a choice of research opportunities, including some not under the investigator. The IRB may require the informed consent form to state whether alternatives are available and what those alternatives are. The investigator must provide assurance that a student's experimental results, performance, or any confidential data will not be given to whomever is grading the student, except for stating whether the student participated or not unless the approved study design provides for

this. Recruitment advertisements need to be approved by the IRB according to previously stated policy. Hospital volunteers are free to participate in research studies, but volunteers working in the investigators own area or lab should be afforded similar protections as described above for students.

Applicable Regulations Procedures

[45 CFR 46.301-306](#)
[VHA Handbook 1200.5](#)

[California Penal Code, Sections 3500-3524](#)

Person(s) Responsible	Procedures
IRB Chair IRB Members	<p>Review the benefits of participation to ensure there are no coercive elements</p> <p>Ensure that the protocol and consent provide adequate protections for vulnerable populations</p> <p>Verify that research is in compliance with federal and institutional directives regarding vulnerable populations</p>
IRB Administrator	<p>Review initial application to ascertain if vulnerable populations are likely to be recruited</p> <p>Secure a voting member who is a prisoner/advocate for reviews of research involving prisoners</p> <p>Secure additional consultants to provide additional expertise on special populations</p>

Review of Projects Involving Pregnant Women

Policy Pregnant Women and Fetuses are considered protected populations, and research must provide the additional protections listed here. Current VA research policy excludes research on pregnant women and fetuses.

Pregnant Women

With regard to research involving the participation of pregnant women as research subjects, the following requirements must be met:

- 1) Appropriate studies on animals and nonpregnant individuals have been completed;
- 2) The purpose of the activity is to meet the health needs of the mother and the fetus will be placed at risk only to the minimum extent necessary to meet such needs or the risk to the fetus is minimal.
- 3) Individuals engaged in the activity will have no part in any decisions as to the timing, method, and procedures used to terminate the pregnancy or determining the viability of the fetus at the termination of the pregnancy.
- 4) No procedural changes that may cause greater than minimal risk to the fetus or the pregnant woman will be introduced into the procedure for terminating the pregnancy solely in the interest of the research activity.
- 5) No inducements, monetary or otherwise, may be offered to terminate pregnancy for purposes of research activity.
- 6) Research activity as described may be conducted only if the mother and father are legally competent and have given their informed consent after having been fully informed regarding possible impact on the fetus, except that the father's informed consent need not be secured if the purpose of the activity is to meet the health needs of the mother, his identity or whereabouts cannot reasonably be ascertained, he is not reasonably available, or the pregnancy resulted from rape.
- 7) The IRB will determine that adequate consideration has been given to the manner in which potential subjects will be selected, and adequate provision has been made to monitor the actual informed consent process such use of consent observers, audits, and/or site visits.

Applicable Regulations [The NIH Revitalization Act of 1993 \(Public Law 103-43\)](#) [Section 498B of the Public Health Service Act \(42 U.S.C. 298g-2\) VHA Handbook 1200.5](#)

Procedures	Person(s) Responsible	Procedures
	IRB Members	Review proposals involving pregnant women

Review of Projects Involving Fetuses or Fetal Tissue

Policy The University of California is compliant with California state law that permits research using human embryonic stem cells if that research is reviewed and approved by a federally registered IRB. However, the VA prohibits research involving a fetus, in-utero or ex-utero (including human fetal tissue) or in vitro fertilization by VA investigators while on official duty or at VA facilities or approved off-site facilities.

Research conducted by UCSD investigators that is funded by federal agencies other than the VA must comply with provisions of the NIH Revitalization Act of 1993 (Public Law 103-43) with respect to use of fetal tissue.

The provisions of that act include the following:

- *Human fetal tissue* means tissue or cells obtained from a dead embryo or fetus after a spontaneous or induced abortion, or after a stillbirth.
- Human fetal tissue may be used regardless of whether the tissue is obtained pursuant to a spontaneous or induced abortion or pursuant to a stillbirth.
- The woman donating the human fetal tissue must sign a statement declaring that the tissue is being donated for therapeutic transplantation research, the donation is being made without any restriction regarding the identity of individuals who may be the recipients of transplantations of the tissue, and the donation is being made without her (the donor) having been informed of the identity of those individuals who may be the recipients.
- The attending physician must sign a statement declaring that the tissue has been obtained in accord with the donor's signed statement and that

full disclosure has been made to the donating woman of: (1) The attending physician's interest, if any, in the research to be conducted with the tissue, and (2) any known medical risks to the donor or risks to her privacy that might be associated with the donation of the tissue and are in addition to the risks associated with the woman's medical care. In the case of tissue obtained pursuant to an induced abortion, the attending physician's statement must also declare that the consent of the woman for the abortion was obtained prior to requesting or obtaining consent for donation, the abortion was conducted in accordance with applicable state law, and no alteration of the timing, method, or procedures used to terminate the pregnancy was made solely for the purposes of obtaining the tissue.

- The individual with the principal responsibility for conducting the research must sign a statement declaring that the individual is aware that the tissue is human fetal tissue donated for research purposes and may have been obtained pursuant to spontaneous or induced abortion or pursuant to a stillbirth; that the principally responsible researcher has provided such information to other individuals with responsibilities regarding the research; that the principally responsible researcher will require, prior to obtaining the consent of a person to be the recipient of a transplantation of the tissue, written acknowledgement of receipt of the foregoing information by such recipient; and that the principally responsible researcher has had no part in any decisions as to the timing, method, or procedure used to terminate the pregnancy made solely for the purposes of the research.
- Research involving the transplantation of human fetal tissue for therapeutic purposes must be conducted in accord with applicable State law and the Secretary may not provide support for such research unless the applicant for assistance agrees to conduct the research. The conduct of such research by the Secretary must be in accord with applicable state and local law.

The provisions of section 498B of the Public Health Service Act (42 U.S.C. 298g-2), added by Public Law 1-3-43, the NIH Revitalization Act of 1993 are summarized as follows:

- It shall be unlawful for any person to knowingly acquire, receive, or otherwise transfer any human fetal tissue for valuable consideration if the transfer affects interstate commerce. (Valuable consideration does not include reasonable payment associated with the transportation, implantation, processing, preservation, quality control, or storage of human fetal tissue.)

- It shall be unlawful for any person to solicit or knowingly acquire, receive, or accept a donation of human fetal tissue for the purposes of transplantation of such tissue into another person if the donation effects interstate commerce, the tissue will be obtained pursuant to an induced abortion, and: (1) The donation will be or is made pursuant to a promise to the donating individual that the donated tissue will be transplanted into a recipient specified by such individual; (2) the donated tissue will be transplanted into a relative of the donating individual; or (3) the person who solicits or knowingly acquires, receives, or accepts the donation has provided valuable consideration for the costs associated with such abortion. (Valuable consideration does not include reasonable payments associated with the transplantation, processing, preservation, quality control or storage of human fetal tissue.)

The IRB, in reviewing research involving fetal tissue that is sponsored by federal agencies, will ensure that all requirements outlined in this section of the guidelines be met. Copies of all the required signed consent documents must be included with the application.

Applicable Regulations Procedures

[The NIH Revitalization Act of 1993 \(Public Law 103-43\)](#)

[Section 498B of the Public Health Service Act \(42 U.S.C. 298g-2\)](#)

Person(s) Responsible	Procedures
IRB Members	Review proposals involving fetal tissue for compliance with applicable federal regulations

Review of Projects Involving Children and Adolescents

Policy Definitions

For purposes of this policy the following definitions are used, consistent with federal and state regulations:

1. "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.
2. "Assent" means a child's affirmative agreement to participate in research. Mere failure to object should not, absent affirmative agreement, be construed as assent.
3. "Permission" means the agreement of parent(s) or guardian to the participation of their child or ward in research.
4. "Guardian" means an individual who is authorized under applicable State or local law to consent on behalf of a child to general medical care.
5. "Emancipated Minor" means a legal status conferred upon persons who have not yet attained the age of legal competency as defined by state law, but who are entitled to treatment as if they had by virtue of assuming adult responsibilities, such as self-support, marriage or procreation.
6. "Mature Minor" means someone who has not reached adulthood (as defined by state law) but who may be treated as an adult for certain purposes (e.g., consenting to medical care). Note that a mature minor is not necessary an emancipated minor.

Policy

Research involving children as subjects must be reviewed by a full Committee regardless of the risks involved, and the committee must have appropriate membership to represent children's interests and pediatric expertise. The IRB reviewing the study has additional responsibilities, to ensure that the study meets all requirements in 45 CFR 46. Subpart D "Additional DHHS Protections for Children Involved as Subjects in research."

Approval letters for research involving children will cite the specific provisions of Subpart D (sections 404-407) under which the approval is given.

For research involving children that is performed using VA support or within VA facilities, VHA Directive 2001-028 states that a waiver must be obtained from the Chief Research and Development Officer in the Central Office. In order for the investigator to obtain this waiver, the IRB minutes should reflect the discussion regarding the level of risk, the consent and assent forms, the investigators' qualifications to conduct research involving children, and any additional safeguards. The Principal Investigator must receive a waiver from the VASDHS R&D committee.

**Applicable
Regulations
Procedures**

[45 CFR 46. Subpart D](#)

[VHA Directive 2001-028](#)

Person(s) Responsible	Procedures
Chair and IRB members	Review research plans and consent documents for compliance with these provisions

Surrogate Consent and Review of Projects Involving Populations with Impaired Decisional Capacity

Policy No person who has the capacity for consent may be enrolled in a study without his or her informed consent.

IRB review of projects involving surrogate consent (as evidenced by a “legally authorized representative” signature line in the consent document) shall conform to the requirements of California law AB2328 that specifies the requirements for and procedures related to the surrogate consent process.

Of note for VA investigators is that VHA Handbook 1200.5 states “Such consent may be requested and accepted only when the prospective research participant is incompetent or has an impaired decision-making capacity, as determined and documented in the person’s medical record in a signed and dated progress note. The determination must be made in accordance with the following requirements in subparagraphs 11a(3)(a-d), or as established by a legal determination. *Note: The consent requirements described in VA Handbook 1200.5 are not intended to preempt any applicable Federal, State or local laws that require additional information to be disclosed for the informed consent to be legally effective in accordance with 38 CFR 16.116(e).*”

The decisional capacity of a potential research subject should be evaluated when there are reasons to believe that the subject may not be capable of making voluntary and informed decisions about research participation. A Decisional Capacity Taskforce, convened in 2001 by the UCSD Department of Psychiatry at the request of the UCSD HRPP, issued investigator guidelines on this topic that are available on the irb.ucsd.edu website.

For research protocols that involve subjects with mental disorders that may affect decision-making capacity, the IRB may determine that capacity assessments are necessary, unless the investigator can justify why such assessments would be unnecessary for a particular group. The requirement for an independent evaluator becomes increasingly justified as the risks to subjects increase.

For research that poses greater than minimal risk, the IRB should generally require investigators to use an appropriate means of determining the potential participant’s capacity to consent. The Decisional Capacity Taskforce guidelines present several alternative approaches for meeting

this requirement. Even in research involving only minimal risk, the IRB may still require that the study include a capacity assessment if there are reasons to believe that potential subjects' capacity may be impaired. It is not necessary to require a formal capacity assessment by an independent professional for all potential research subjects with mental disorders.

For research protocols involving subjects who have fluctuating or limited decision-making capacity the IRB should ensure that investigators establish and maintain ongoing communication with involved caregivers. Periodic re-consent should be considered in some cases. Third party consent monitors may be used during the recruitment and consenting process, or waiting periods may be required to allow more time for the subject to consider the information that has been presented.

It is often possible for investigators and others to enable persons with some decisional impairments to make voluntary and informed decisions to consent or refuse participation in research. Potential measures include repetitive teaching, group sessions, audiovisual presentations, and oral or written recall tests. Other measure might include follow-up questions to assess subject understanding, videotaping or audio-taping of consent interviews, second opinions, use of independent consent observers, or involvement and/or concurrent consent of a trusted family member or friend in the disclosure and decision-making process.

Determination of decisional capacity

Decisional capacity in the research context has been interpreted by the American Psychiatric Association as requiring:

- 1) ability to evidence a choice;
- 2) ability to understand relevant information;
- 3) ability to appreciate the situation and its likely consequences; and
- 4) ability to manipulate information rationally.

A range of professionals and methods may be utilized to assess capacity. In general the consent assessor should be a researcher or consultant familiar with dementias and qualified to assess and monitor capacity and consent in such subjects on an ongoing basis. The IRB will consider the qualifications of the proposed individual(s) and whether he or she is sufficiently independent of the research team and/or institution.

The protocol should describe who will conduct the assessment, the method by which prospective subjects' decisional capacity will be evaluated, and the criteria for identifying incapable subjects. Less formal procedures to assess potential subjects' capacity may be permitted if a formal assessment

is not feasible. Less formal procedures could include the ways professionals often make judgments about capacity in routine interactions.

Surrogate Consent

California law AB2328, codified as California Health & Safety Code Section 24178 became effective January 1, 2003 and clarifies who may serve as a research subject's "legally authorized representative." The IRB review of a new or revised application that proposes to have the option of consent by surrogates will address the project's compliance with the provisions of state law as noted below.

Surrogate consent may be considered only in research studies relating to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and conditions of research subject. The investigator shall include in the IRB application/modification form a protocol-specific plan for the sequence of steps that will be employed to acquire and document surrogate consent provided by a legally authorized representative. These steps include the following:

1. Whenever possible, investigators will attempt to obtain informed consent directly from the subject.
2. If the potential research subject is obtunded, unconscious or otherwise obviously lacking in decision-making capacity, the investigator shall:
 - a) Document that observation in the research record and in the subject's medical record;
 - b) Proceed with the steps listed below under *Identifying Persons to Provide Surrogate Consent*
3. If the potential research subject has questionable capacity to consent but is not unresponsive, the investigator shall:
 - a) Consistent with the standard consent process, describe the research to the subject;
 - b) Perform and document an assessment of the participant's decisional-capacity relevant to the information provided about the research study;
 - c) If lack of decisional capacity is evident, the investigator shall inform the potential research subject of the investigator's intent to obtain surrogate consent;
 - d) If the subject expresses resistance or dissent to participation or to the use of surrogate consent by word or gesture, the subject shall be excluded from the research study.
 - e) If no resistance or dissent is expressed by the potential

research subject, the investigator shall document this fact, and document that the description of the research project was communicated to the subject by placing a note in the medical record and in the research record.

- f) Proceed with the steps listed below under *Identifying and Informing Persons providing Surrogate Consent*

Identifying Persons to Provide Surrogate Consent

In a non-emergency room environment, surrogate consent may be obtained from any of the following potential surrogates who has reasonable knowledge of the subject, in the following descending order of priority:

1. The person's agent designated by an advance health care directive.
2. The conservator or guardian of the person having the authority to make health care decisions for the person.
3. The spouse of the person.
4. The domestic partner of the person as defined in Section 297 of the Family Code
5. An adult son or daughter of the person.
6. A custodial parent of the person.
7. Any adult brother or sister of the person.
8. Any adult grandchild of the person.
9. An available adult relative with the closest degree of kinship to the person.

In non-emergency room research settings, no surrogate consent may be utilized if there is a disagreement whether to consent among the members of the highest available priority class of surrogates, (e.g., where two members of persons in the highest of categories (5) – (7) disagree and there is no person in categories (1) – (4) available.

In non-emergency room research settings only, the investigator is responsible for ensuring that the surrogate:

- Has reasonable knowledge of the subject;
- Is familiar with the subject's degree of impairment;
- Is willing to serve as the substitute decision-maker;
- Understands the risks, potential benefits, procedures and available alternatives to research participation;
- Makes their decisions based on the subject's known preferences, and where the subject's preferences are unknown, makes decisions based upon the surrogate's judgment of what the subject's preferences would be if different from their own.

In an emergency room setting, the order of priority does not apply, nor does the surrogate have to show reasonable knowledge of the subject. Surrogate consent may be obtained from a surrogate decision maker who is any of the following:

1. The person's agent designated by an advance health care directive.
2. The conservator or guardian of the person having the authority to make health care decisions for the person.
3. The spouse of the person.
4. The domestic partner of the person as defined in Section 297 of the Family Code.
5. An adult son or daughter of the person.
6. A custodial parent of the person.
7. Any adult brother or sister of the person.

In emergency room research settings, *no surrogate consent may be utilized if there is a disagreement whether to consent among any available surrogates.*

Obtaining Consent from the Surrogate

1. Investigators shall describe to potential surrogates the nature of ongoing decisions during the study regarding the subject's participation, decision to participate in certain procedures, changes to the study, etc., in order to ensure that the surrogate will be willing to undertake these on-going responsibilities.
2. The surrogate shall complete the "*Self-Certification of Surrogate Decision Makers for Participation in Research*" form as an attachment to the informed consent document for the research study, and be given a copy of this form along with a copy of the consent to keep. In addition, the researcher must keep the signed form in the research records along with the signed consent. The "*Self-Certification of Surrogate Decision Makers for Participation in Research*" form verifies the willingness of the person to serve as a surrogate, details the relationship of the surrogate to the subject and the surrogate's qualifications demonstrating "reasonable knowledge" of the research subject. (Note: Section 3 of the "*Self-Certification of Surrogate Decision Makers for Participation in Research*" form is required only for surrogate consent in non-emergency room environment settings).
3. Potential surrogates must be advised that if a higher-ranking surrogate is identified at any time, the investigator will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.
4. For non-emergency room environment research only, if the

potential surrogate identifies a person of a higher degree of surrogacy, the investigator is responsible to contact such individuals to determine if they want to serve as surrogate.

5. Surrogates are prohibited from receiving any financial compensation for providing consent. This does not prohibit the surrogate from being reimbursed for expenses the surrogate may incur related to the surrogate's participation in the research.
6. Assessment of the decision-making capacity *of the surrogate* should be implemented only when the investigator has reason to believe that the surrogate's decision-making capacity may be impaired.

NOTE: Surrogate consent to participate in research under California Health & Safety Code section 24178 **is not permitted** for persons in a State of California mental health facility inpatient psychiatric ward, or persons on psychiatric hold. This is more restrictive than the standard under previously existing law whereby an incapacitated adult with a conservator or guardian could be enrolled onto a study being conducted in an inpatient psychiatric unit because conservators and guardians were considered legally-authorized representatives.

Re-consenting of Research Subjects

Consenting is an ongoing process. All applicable criteria that would trigger re-consenting a subject in any study shall apply to subjects whose consent has been provided by a surrogate. In addition:

- A subject who regains the cognitive ability to consent must be re-consented using standard consenting procedures.
- In the event a subject has been initially consented by a surrogate, and a surrogate of higher priority subsequently notifies the investigator of that relationship to the subject, the investigator must defer to the higher priority surrogate's decision regarding whether the subject will continue to participate or to withdraw from the study.
- Investigators shall describe to potential surrogates the nature of ongoing decisions during the study regarding the subject's participation, decision to participate in certain procedures, changes to the study, etc., in order to ensure that the surrogate will be willing to undertake these on-going responsibilities.

In the event that the surrogate dies, the subject must be re-consented subsequently upon any event that would otherwise trigger re-consenting the subject.

The IRB letter of approval will specifically document that the project complies with the provisions of California law for use of surrogate consent.

Applicable Regulations [VHA Handbook 1200.5](#) [American Psychiatric Association, "Guidelines for Assessing the Decision-making Capacities of Potential Research Subjects with Cognitive Impairments," American Journal of Psychiatry 155 \(1998\): 1649–50.](#)
[California Health and Safety Code, Section 24175](#)
[National Bioethics Advisory Commission. Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity, December 1998.](#)

Procedures

Person(s) Responsible	Procedures
IRB Chair and Reviewer(s)	Determine what human subjects protections are appropriate to a study and to the needs of decision-impaired individuals, according to this policy. Verify during continuing review that the policy has been followed.
Investigator	Select appropriate individuals and methods for capacity determinations
IRB Administrator	Document in the file that additional approval criteria in this section have been met.

Financial Disclosure and Conflict of Interest

Policy A. Financial Disclosure and Conflict of Interest for IRB Members

No regular or alternate member may participate in the initial or continuing review of any project in which the member has a significant financial interest or a conflict of interest, except to provide information as requested. The policy pertains to interests in business, non-profit and public entities in an area related to the research, where the entity could reasonably appear to affect or be affected by the review, conduct, or reporting of the sponsored project. A conflict of interest is defined as direct participation in the research (e.g., protocol development, principal or subinvestigator), or any significant financial interest in the sponsoring company. A potential conflict of interest may also be present when there is close professional, personal, or financial relationship between an IRB member and an investigator. In such cases, the IRB member must disclose

such a relationship to the committee prior to discussion of the relevant issue, or may choose to recuse him or herself from participation in the discussion. Final determination of the presence of an IRB member's conflict of interest and a plan for its management will reside with the IRB Chair, in consultation with the IRB Administrator, and if appropriate, the UCSD and VASDHS Conflict of Interest offices.

Each IRB member must disclose any business or professional relationships that may represent a conflict of interest or an appearance of conflict of interest in a particular company, their product(s), data, or method(s). This disclosure should be given orally and reflected in the meeting minutes for all project reviews where it is relevant.

B. Financial Disclosure and Conflict of Interest for Investigators

The principal investigator and all subinvestigators must report all actual or potential significant financial interests and any conflicts of interest for partially or fully commercially sponsored studies to the campus Conflict of Interest program office using California Form 700-U, available online from the UCSD Office of Grants and Contracts website (<http://ocga.ucsd.edu>). This disclosure policy applies to the principal investigator, subinvestigators, and all personnel responsible for the design, conduct or reporting of the study. The policy pertains to interests in business, non-profit and public entities in an area related to the research, where the entity could reasonably appear to affect or be affected by the design, conduct, or reporting of the sponsored project. The IRB takes into consideration whether the potential conflicts of interests might adversely affect subject welfare. The UCSD and VASDHS IRCs work with the investigator to take steps to manage, reduce or eliminate the conflict.

Thresholds for disclosure of financial conflicts of interest in all cases will conform at least to the federal guidelines for PHS grants. However, disclosure standards of other agencies (FDA, PHS, OHRP, commercial sponsor, state, or University of California) must also be met in some cases, if they have authority over a project. If the project will be externally funded, the Principal Investigator will have completed the appropriate financial disclosure forms of the funding agency and stated if a COI was indicated there.

C. Review and Management of Conflicts of Interest

During the initial review process, the IRB will review any potential conflicts of interest that may be present. If the IRB determines that the investigator's financial or other interest could adversely affect subject

welfare, the IRB will take appropriate action to approve, disapprove, or require modifications to reduce the conflict and inform study participants. For VA investigators, the matter will also be reviewed by the VA Independent Review Committee (IRC) for further action as per VASDHS institutional policy.

The UCSD Conflict of Interest program office will also conduct committee-based evaluations of conflict of interest issues and communicate their determinations to the UCSD HRPP. These may result in modifications to research plan or consent documents after initial IRB approval, since the IRB review process tends to complete sooner than conflict of interest reviews.

**Applicable
Regulations
Procedures**

[42 CFR 50.601-607](#)
[21 CFR 54.4-6](#)

Person(s) Responsible	Procedures
IRB Members, including Chair and alternates	Report COIs and potential COIs during meeting discussions
IRB Administrator or staff designee	Review and approve minutes containing discussions of COI issues Oversee disclosure in consent documents

Exemption from IRB review

Policy

The “Common Rule” (45 CFR 46 subpart A) defines a set of research activities that may be exempt from its purview, unless otherwise required by Department or Agency heads. The UCSD IRBs **do not recognize** these exempt categories, thus research activities that would otherwise be exempt under these federally-defined categories must be submitted for IRB review. In most cases these activities would qualify for expedited review procedures. These research activities, as defined by 45 CFR 46.101(b), include:

- (1) Research conducted in established or commonly accepted educational settings, involving normal educational practices, such as (i) research on regular and special education instructional strategies, or (ii) research on the effectiveness of or the comparison among instructional techniques, curricula, or classroom management methods.
- (2) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures or observation of public behavior, unless:
(i) information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and (ii) any disclosure of the human subjects' responses outside the research could reasonably place the subjects at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, or reputation.
- (3) Research involving the use of educational tests (cognitive, diagnostic, aptitude, achievement), survey procedures, interview procedures, or observation of public behavior that is not exempt under paragraph (b)(2) of this section, if:
(i) the human subjects are elected or appointed public officials or candidates for public office; or (ii) Federal statute(s) require(s) without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter.
- (4) Research involving the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens, if these sources are publicly available or if the information is recorded by the investigator in such a manner that subjects cannot be identified, directly or through identifiers linked to the subjects.

- (5) Research and demonstration projects which are conducted by or subject to the approval of Department or Agency heads, and which are designed to study, evaluate, or otherwise examine:
- (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.
- (6) Taste and food quality evaluation and consumer acceptance studies, (i) if wholesome foods without additives are consumed or (ii) if a food is consumed that contains a food ingredient at or below the level and for a use found to be safe, or agricultural chemical or environmental contaminant at or below the level found to be safe, by the Food and Drug Administration or approved by the Environmental Protection Agency or the Food Safety and Inspection Service of the U.S. Department of Agriculture.

[45 CFR 46.101\(b\)](#)

Applicable Regulations Procedures

Person(s) Responsible	Procedures
IRB Administrator or designee	Provide educational materials for investigators and committee members that inform them of institutional policy regarding review of research in the categories listed.

Expedited Review

Policy

The expedited review process consists of a review of research involving human subjects by the IRB Chair or by one or more experienced reviewers designated by the Chair from among members of the IRB. Such designees must have demonstrated familiarity with the scope of the research as well as a sound grasp of the relevant regulations and policies. Research reviewed by the expedited review process will undergo the same careful review by its reviewer as one subjected to full review. A determination may be made that full committee review is required although the criteria below is met.

A. Categories of Research Appropriate for Expedited Review

New Studies

The categories of research that may be reviewed by the IRB through an expedited review process include research activities that (1) present no more than minimal risk or discomfort to human subjects, and (2) involve only procedures in one or more of the categories listed below. Minimal risk is defined in 45CFR 46.102(i) and 21CFR56.102(i) as "...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...". This assessment should take into account both the likelihood of harm and the severity of that harm if it occurs.

The activities listed should not be deemed to be of minimal risk simply because they are included on this list. Inclusion on this list merely means that the activity is eligible for review through the expedited review process when the specific circumstances of the proposed research involve no more than minimal risk or discomfort to human subjects. The categories in this list apply regardless of the age of subjects, except as noted. The categories listed pertain to both initial and continuing IRB review:

- (1) Clinical studies of drugs and medical devices only when condition (a) or (b) is met.
 - (a) Research on drugs for which an investigational new drug application (21 CFR 312) is not required. Research on marketed drugs that significantly increases the risks or decreases the acceptability of the risks associated with use of the product is not eligible for expedited review.

- (b) Research on medical devices for which (i) an investigational device exemption application (21 CFR 812) is not required; or (ii) the medical device is cleared/approved for marketing and the medical device is being used in accordance with its cleared/ approved labeling
- (2) Collection of blood samples by finger heel or ear stick, or venipuncture, as restricted in: (a) from healthy, non-pregnant adults who weigh at least 110 lbs. The amounts drawn may not exceed 550 ml in an 8 week period and collection may not occur more frequently than 2 times per week. (b) from other adults and children, considering the age, weight, and health of the subjects, the collection procedure, the amount of blood to be collected, the frequency with which it will be collected. For these subjects, the amount drawn may not exceed the lesser of 50 ml or 3 ml per kg in an 8 week period and collection may not occur more frequently than 2 times per week.
- (3) Prospective collection of biological specimens for research purposes by noninvasive means, including: (a) Hair and nail clippings in a non-disfiguring manner. (b) Deciduous teeth at time of exfoliation or if routine patient care indicates a need for extraction. (c) Permanent teeth if routine patient care indicates a need for extraction. (d) Excreta and external secretions (including sweat). (e) Uncannulated saliva collected either in an unstimulated fashion or stimulated by chewing gumbase or wax or by applying a dilute citric solution to the tongue. (f) Placenta removed at delivery. (g) Amniotic fluid obtained at the time of rupture of the membrane prior to or during labor. (h) Supra- and subgingival dental plaque and calculus, provided the collection procedure is not more invasive than routine prophylactic scaling of the teeth and is accomplished in accordance with accepted techniques. (i) Mucosal and skin cells collected by buccal scraping or swab, skin swab, or mouth washings. (j) Sputum collected after saline mist nebulization.
- (4) Collection of data through noninvasive procedures (not involving general anesthesia or sedation) routinely employed in clinical practice, excluding procedures involving x-rays or microwaves. Where medical devices are employed, they must be cleared/ approved for marketing. Note: Studies to evaluate the safety and effectiveness of the medical device are not generally eligible for expedited review, including studies of cleared medical devices for new indications.
 - (a) Physical sensors that are applied either to the surface of the body or at a distance and do not involve input of significant amounts of

energy into the subject or an invasion of the subject's privacy.

- (b) Weighing or testing sensory acuity.
 - (c) Magnetic resonance imaging.
 - (d) Electrocardiography, electroencephalography, thermography, detection of naturally occurring radioactivity, electroretinography, ultrasound, diagnostic infrared imaging, Doppler blood flow, and echocardiography.
 - (e) Moderate exercise, muscular strength testing, body composition assessment, and flexibility testing where appropriate given the age, weight, and health of the individual.
- (5) Research involving materials (data, documents, records, or specimens) that have been collected or will be collected solely for nonresearch purposes (such as medical treatment or diagnosis).
- (6) Collection of data from voice, video, digital, or image recordings made for research purposes.
- (7) Research on individual or group characteristics or behavior (including, but not limited to, research on perception, cognition, motivation, identity, language, communication, cultural beliefs or practices, and social behavior) or research employing survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies.

The expedited review process may not be used where identification of the subjects and/or their responses would reasonably place them at risk of criminal or civil liability or be damaging to the subjects' financial standing, employability, insurability, reputation, or be stigmatizing, unless reasonable and appropriate protections will be implemented so that risks related to invasion of privacy and breach of confidentiality are no greater than minimal. Furthermore, the expedited review process may not be used for classified research involving human subjects. The expedited review process may not be used for procedures involving collection of samples for genetic analysis, unless collected anonymously.

When an investigational device meeting Non Significant Risk (NSR) criteria is used in a study that also meets minimal risk criteria, the study may be reviewed by the expedited review process. NSR medical device research not meeting minimal risk criteria will be reviewed by the full IRB. If the IRB reviews the research, the IRB also will make the final determination to concur or not concur with the sponsor's assessment of the device's non-significant or significant risk status.

2. Minor Changes in Approved Studies and Informed Consent Documents

In some cases the Chair or his/her designee may use the expedited review process to approve minor changes to previously approved human research procedures or informed consent documents during the period for which approval is authorized. This is only possible if the changes do not affect the rights and welfare of study subjects, do not have the potential to increase risk to study subjects, and do not involve significant changes in study procedures. Any revision that entails any increase in risk or discomfort to the participants, or which substantively changes the study design or study procedures, must be reviewed by the full IRB at a convened meeting.

3. Continuing Review, Interim and Completion Reports

Continuing Review conducted at the intervals not greater than 365 days from the most recent project approval. Interim and Completion Reports may be reviewed using the expedited review process only if:

- (a) the research is permanently closed to the enrollment of new subjects, all subjects have completed all research-related interventions, and the research remains active only for long-term follow-up of subjects; or
- (b) no subjects have been enrolled and no additional risks have been identified; or
- (c) the remaining research activities are limited to data analysis; or
- (d) for research not conducted under an investigational new drug application or investigational device exemption where 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; or
- (e) the research initially qualified for expedited review and there have been no changes that would increase the risk.

4. Modifications Required to Secure Approval

Minor revisions to the informed consent and other documents and clarifications submitted in response to initial IRB review as a condition for approval may be reviewed by expedited review, if determined by the IRB at the time of initial review. The Chair, his/her designee, or the primary reviewer will review the modifications and determine whether the requirements of the IRB have been met. Approval can be issued providing the revisions, documentation or clarifications do not indicate or result in a substantive change to the study design and procedures or change the risk/benefit ratio.

5. Modifications in advertisements

The Chair or his/her designee may approve minor modifications to approved recruitment advertisements using the expedited review process.

6. Serious Adverse Event and Safety Reports

The Chair or a member designated by the Chair (such as the original primary reviewer, if available) may review Serious Adverse Events Reports (including IND Safety Reports) by expedited review.

8. Translations

Translations of consent forms and other documents submitted for IRB approval may be reviewed by an expedited review process provided one of the following procedures are followed:

- a) The IRB-approved consent form is translated by the sponsor or site and submitted to the IRB. The IRB will have a member or consultant fluent in the language of the consent review the translated document for accuracy. It must match the English version; or
- b) The sponsor or investigator may submit the IRB-approved version of the consent to a certified translator or individual with sufficient expertise for translation. Written documentation attesting to the accuracy, such as the proof of certification, is also required.
- c) While a translator may be used to facilitate conversation with the subject, routine ad hoc translation of the consent document may not be substituted for a written translation.

B. Expedited Review Process

The Chair or designee can require full review of any research at his/her discretion, even if the research would otherwise qualify for expedited review status. The decision to actually grant expedited review status is initially made by the Chair or designee. If it is determined that expedited review is appropriate for a study or one of the other activities described above, and the Chair or designee wishes to utilize this procedure, the Chair or designee will document his/her determination of risk. The review is then performed by one or more experienced members designated by the Chair. The Chair or designee may exercise all of the authorities of the IRB, except that he/she may not disapprove the research. A research proposal may be disapproved only after review by the IRB at a convened meeting. The Chair is encouraged to use the expedited review process judiciously.

When the expedited review process is used for initial review, continuing

review, or completion reports, the IRB members will be informed of actions taken by the IRB Chair or designee at the next convened meeting. At that time the members will have the opportunity to further review, discuss, perform full review, disapprove, or require modifications.

All review requirements and approval criteria for initial and continuing review described elsewhere in these SOPPs continue to apply to research reviewed under the expedited review process.

Applicable Regulations

[21 CFR 56.110](#),
[45 CFR 46.110](#)
[38 CFR 16.110](#)

Federal Register Vol. 63, No. 216,
 11/9/98, pp. 60353-60356

Procedures

Person(s) Responsible	Procedures
IRB Administrator or designee	<p>Review new submissions requesting expedited review to determine if they qualify for expedited review.</p> <p>Prepare and distribute summary of expedited review actions to IRB members at next convened meeting.</p> <p>Document discussions of actions in minutes.</p>
IRB Chair or designee	<p>Confirm and approve determination that submission qualified for expedited review on Expedited Review Determination form.</p> <p>Make and document determination of minimal risk research.</p> <p>Designate an appropriate IRB member (including self) to conduct the expedited review.</p>
Designated Reviewer	<p>Conduct review (including protocol, informed consent form) and document on Expedited Review Worksheet</p>

Continuing Review

Policy The UCSD HRPP limits all project approvals to an initial approval period of 12 months, and upon continuing review to an additional approval period not to exceed 12 months. After 24 months all projects must be resubmitted in full for Initial Review. This policy has served well over the past decade due to the rapid evolution of scientific methods. Investigators are required to submit a **Annual Continuing Review Form** not later than 14 days prior to the continuing review deadline. The continuing review form is used as 1) a request for reapproval of ongoing research where annual (or more frequent) review is required, 2) a final report to be used when research has been completed or terminated, or 3) an interim report (an IRB-required report of study progress that is not required for reapproval). Continuing review actions will be carried out at a convened IRB meeting, except in those cases where expedited review is permitted.

A. Interim Reports

If the IRB determines that a study requires an Interim Report, the investigator may be asked to submit an application for continuing review and reapproval by a specified date, upon enrollment of a specified number of subjects, or upon reaching a specified point in the study. If interim reports are not received as scheduled, the IRB may suspend enrollment until reports are reviewed. The IRB will review the Interim Report, and if appropriate the continuing review form, at a convened meeting, and may require modifications or take other actions within its authority.

B. Reapprovals

Investigators may not continue to conduct their investigations beyond the continuing review deadline. Studies that have expired before the form has been reviewed will be suspended until the IRB review has been conducted. UCSD HRPP will provide assistance to investigators in the form of deadline reminders and online status information for investigators, and will issue a letter within 30 days of protocol lapse or expiration stating affirmatively that the study no longer has IRB approval and research activities must cease. However, if the investigator is in communication with the IRB at the time of approval expiration, the information regarding conduct of the study is forthcoming, and, in the opinion of the Chair, the subjects participating in such a study would suffer a hardship if medical care were discontinued, appropriate medical care may continue beyond the expiration date for a reasonable amount of time. However, new subjects

cannot be enrolled and the data acquired during the period of lapse of IRB approval may not be used for analysis or publication.

C. Completion Reports

A notice of study completion should be submitted by the Principal Investigator to the UCSD HRPP within 60 days after completion or termination of the study. A study may be considered completed once all interactions with human subjects and all data collection from human subjects, including subject follow up, have been completed. Additional reports information about the status of the study, such as computer printouts, telephone reports, sponsor's completion summary, letter, etc. may be submitted. The Chair or a designated reviewer will review the report.

D. Reporting of Adverse Events / IND Safety Reports

Investigators are required to report Adverse Events which are serious (SAEs), or which are unexpected and are associated with the research procedures or investigative product. This applies whether the events occur at local or at outside sites in a multicenter study. Investigators will also report to the IRB:

- other unexpected events related to the safety of subjects,
- all significant deviations from the protocol, good clinical practice, applicable regulations or institutional policies involving the conduct of the study or subject participation,
- summaries of the DSMB findings, if a DSMB is used,
- other types of adverse events, as defined by the monitoring plan in the protocol or in FDA regulations or other applicable federal regulations.

The investigator will submit reports of adverse events occurring at the investigators own site on the UCSD Serious Adverse Event Form, or via the online Adverse Event Reporting system available at <http://irb.ucsd.edu>. A separate report must be submitted for each incident. In the report the principal investigator will indicate the nature of the event, whether, in the investigator's opinion, the adverse event was related to the research activity, why the investigator holds this opinion, and whether changes in the protocol and/or consent form are warranted.

All fatal or immediately life-threatening events must be reported in writing to the IRB as soon as possible, but no later than 10 working days after discovery. The report should include copies of any reports sent to the study sponsor or FDA. Other types of adverse events must be reported within 10 working days of awareness of the problem.

Reports of adverse events occurring at non-local sites will be submitted with a cover letter or memo containing the reference number of the report(s) and a signed statement by the investigator that he/she has reviewed the events and whether he/she feels that any modifications are required in the protocol or consent. These adverse events must be reported within 10 working days of receipt.

Serious Adverse Events Reports (including IND Safety Reports) from both local and non-local sites will be reviewed by the Chair or designee. The reviewer may recommend to the Chair that the report be accepted or that it undergo full IRB review. If the Chair or his/her designee determines that the risk of the study may have changed, that the consent form may require modification, or that further action may be needed to protect the safety of research subjects (e.g.: unexpected nature or frequency of reported adverse events), the Chair will take immediate actions as needed and the report will be forwarded to the IRB to be discussed at a convened meeting. Based upon this review, the IRB may reconsider its approval of the study, require modifications to the study and/or informed consent form, revise the continuing review timetable, or require notification and/or re-consent of subjects already enrolled in the study.

The IRB must also ensure that reports of unanticipated problems involving risks to human subjects or others, instances of serious or continuing noncompliance with this Handbook or the determinations of the IRB, and suspension or termination of IRB approval are reported to FDA, ORO, OHRP, and/or institutional officials according to the requirements of each agency. Usually, this reporting is accomplished through the normal reporting channel, i.e., the investigator to the sponsor to FDA.

For VA studies, any serious adverse reaction related to a procedure or treatment arising from a research protocol will be reported on VA Form 2633 "Report of Special Incident Involving a Beneficiary" to the VA Performance Improvement Management Service (PIMS) and to the ACOS R&D. It is essential that all serious adverse outcomes at VASDHS be reported immediately via this mechanism.

E. Process for Conducting Continuing Review

When reviewing a project for reapproval, the IRB will assess all of the same criteria for approval that were evaluated during initial review.

Routine continuing review will include review of available sources of information pertinent to the assessment of risks and benefits, including:

- Annual Continuing Review Form and other materials on file or

submitted by the investigator. The application should contain sufficient information permit determination of the current risk-benefit assessment based on study results. Special attention should be paid to determining whether new information or unanticipated risks were discovered since the previous IRB review. Any significant new findings that may relate to the subjects' willingness to continue participation should also be included.

- The consent document currently in use to ensure that the document has current IRB approval and to determine whether the information contained in it is still accurate and complete, including whether new information that may have been obtained during the course of the study needs to be added.
- A copy of the study protocol currently in use.
- Approved or proposed amendments, including minor changes, (if any) and the IRB action on each amendment.
- Number of subjects enrolled in the study.
- Research findings to date.
- Adverse event reports from investigators, sponsor safety reports (e.g., IND or IDE Safety Reports).
- Documentation of protocol violations and/or deviations, or non-compliance with applicable regulations in the study file.
- All reports of injuries to subjects, unanticipated problems, complaints from subjects or others, or any information that may change the risk/benefit ratio for subjects.
- A statement from the investigator that all SAEs and unexpected adverse drug experiences have been reported as required.
- Amended or updated Investigator Brochures.
- Review of a summary of the Data Safety Monitoring Board (DSMB) meetings (if applicable) or findings based on information collected on AEs and SAEs as required by the approved data and safety monitoring plan.
- Any new recruitment documents.
- In addition to copies of the documents required for continuing review, the IRB may consider the following information, where applicable, for continuing review:

- a) Recent published medical or scientific studies applicable to the protocol.
- b) Number, gender, and minority status of subjects enrolled and entered into the study.
- c) Number of subjects considered to part of a vulnerable population.

Based on its review of the above information the IRB determines for each approved research protocol whether the research is reapproved, requires modifications to secure reapproval, is suspended or disapproved (terminated). The IRB may also require appropriate changes to the informed consent form content, frequency of continuing review, level of safety monitoring, and may determine whether the project requires verification from sources other than the investigator that no material changes have occurred since previous IRB review. The IRB will vote upon the recommendations made by the reviewers, and will determine the frequency of review.

Reports of the continuing review process will be reported in a timely manner to the investigator, the VA R&D Committee, and institutional officials as required.

Applicable Regulations

[21 CFR 56.109 \(f\)](#)
[21 CFR 812.150\(a\)\(6\)](#)[38 CFR 16.109 \(e\)](#)
[45 CFR 46. 109\(e\)](#)[21 CFR 56.110\(b\)](#)
[21 CFR 56.108\(a\)\(4\)](#)

[21 CFR 56.108\(b\)\(1\)](#)
[21 CFR 50.25\(b\)\(5\)](#)
[OHRP Guidance, IRB Approval Periods and Continuing Review of Research, October 20,2000](#)

Procedures

Person(s) Responsible	Procedures
<p>IRB Chair IRB Members</p>	<p>Project Reviews</p> <p>Review the information in forms submitted for continuing review, adverse experience reports submitted by the investigator, proposed revisions to the approved research protocol, if any, and any significant new findings which may affect the welfare and safety of the subjects</p> <p>Review the consent form and update it if needed based upon review of above items</p> <p>Review any other pertinent reports in the study file (e.g.: audit reports, correspondence, complaints, etc.)</p> <p>Vote on a category of action.</p> <p>Adverse Event Reports</p> <p>Review reports promptly, determine whether changes in protocol or consent may be necessary, determine which reports will be reviewed by full IRB, take initial action as needed to ensure subject welfare</p>
<p>IRB Administrator or staff designee</p>	<p>Check Interim, Renewal and Completion Reports for completeness</p> <p>Request further information from the investigator to clarify any questions, as needed</p> <p>Make copies of reports available to IRB members prior to next convened meeting</p> <p>Notify members of continuing review actions by the Chair or designee using expedited review process</p> <p>Notify investigators of reapproval and other report submission deadlines</p> <p>Maintain documentation of any new significant findings relevant to study subjects and how the information was provided.</p>

References Continuing Review Monitoring and Renewal form
Forms and Adverse Event Report Form
Links

Protocol Amendments

Policy All modifications/amendments to an approved application and/or consent form must be received and approved by the IRB before they are initiated except where necessary to eliminate apparent immediate hazard to the study participants, as provided in Subpart C, 56.108(a)(4) of the federal regulations. In cases where a protocol is amended to eliminate apparent immediate hazard, the changes made must be reported to the IRB promptly, and a review of the changes will be conducted. Requests for approval of modifications may be submitted at any time. Amendments to the sponsor's Master Protocol and amendments to the Investigator's Brochure must also be reviewed.

Major modifications/amendments are reviewed through the full committee review process, minor modification requests through the expedited process. Examples of modifications considered to be major in nature include, but are not limited to, escalation in the drugs(s) dosage(s), the introduction of an additional drug(s); the addition of a new invasive procedure. Major modifications may impact on the risk/benefit ratio in the study. It is the investigator's responsibility to assess the degree of change in procedures and risks of the study.

The initial determination as to whether a modification is major or minor is the responsibility of the principal investigator, who assesses the degree of change in procedures and risks. However, the acceptance of the determination rests with the IRB. The modification is reviewed by the IRB professional staff and a determination of whether full IRB review is necessary is made.

Minor changes in previously approved research during the period (of 1 year or less) for which approval has been authorized will be done under an expedited review process. The review will be carried out by the IRB Chair, or his/her designee(s) from members of the IRB. If the Chair or designee believes that the "minor" modification is too substantive to receive this type of review, the application will be referred for full IRB review. A modification is given approval only to the expiration date that was received at the most recent initial or renewal review.

Changes in study sites or investigators or additions must also be reported

to the IRB. These requested changes involve sending a cover letter, revised application face page, and may involve revised research plans and consent documents. In the case of a change in the principal investigator, the letter should be signed by the investigator who holds the approval.

Applicable Regulations [45 CFR 46 Subpart C](#)
[21 CFR 56.108\(a\)\(4\)](#)

Adverse Event Reporting

Policy The United States Food and Drug Administration under Subpart C - IRB Functions and Operations 56.108 Subpart C (b)(1) requires written procedures for ensuring prompt reporting to the IRB, appropriate institutional officials, and the FDA of any instance of serious or continuing problems involving risks to human subjects or others. This institution includes the notification of this requirement on the cover sheet for all IRB approval letters.

The HRPP office must be notified in writing of any injuries to human subjects and/or any unanticipated problems that involve risks to human subjects or others. Title 21 of the Code of Federal Regulations and the HRPP require that a report be made of unexpected, fatal or life-threatening experiences in writing no later than **10 working days** of the event. Investigators may use either paper adverse event reporting forms, or HRPP's online Adverse Event Reporting system to submit reports. The use of the online system is preferred because upon receipt of a new Adverse Event report the system automatically notifies relevant research oversight offices such as the Central Clinical Trials office, General Clinical Research Center, and Cancer Center depending upon the characteristics of the protocol.

Confidentiality, for both subjects and investigators, to the extent allowed by law will be maintained in the reporting of adverse events.

The written report of the adverse event submitted by the investigator will be presented to the IRB. If additional information is required by the IRB in order to make a final determination concerning the event, the investigator will receive such a request in writing from the Committee. In addition, and if necessary, the IRB may directly audit the research and medical records pertaining to the event or interview witnesses.

Unanticipated problems involving risks to human subjects or others will be promptly reported to OHRP, FDA, and the appropriate University officials. IRB committees may additionally require that such problems be communicated to the other participants in the study, and that all study participants be re-consented if the information regarding risks would be

reasonably expected to affect their willingness to continue in the study.

The Director, Human Research Protections Program, is responsible for reporting unanticipated problems involving serious risks to subjects, instances of serious or continuing noncompliance with regulations or committee requirements, and any suspension or termination or committee approval, to the US Food and Drug Administration, OHRP and appropriate institutional officials, in compliance with guidance provided by federal regulations and University policy.

Applicable Regulations [21 CFR 56.108 Subpart C](#)

Procedures	Person(s) Responsible	Procedures
	Principal Investigator	Submits SAE reports in a timely fashion to the HRPP
	IRB Administrator	Reports unanticipated problems involving risks to subjects, instances of serious or continuing noncompliance with regulations or committee requirements, and any suspension or termination or committee approval, to the US Food and Drug Administration, OHRP and appropriate institutional officials in compliance with federal regulations and institutional policies.

References Forms and Links UCSD Subject Injury Report Form

Protocol and Regulatory Violations

Policy Protocol Violations

Investigators are required to conduct their research according to the plans reviewed and approved by the IRB. Instances where this does not occur, either inadvertently due to circumstances beyond the investigator’s control, or due to errors of omission or commission by research project staff, must be reported to the IRB in a timely fashion. Normally this will be within 30 days of the event, unless subject injury has resulted. In cases of harm to participants, events should be reported to the HRPP program office within one business day, and to project sponsors per sponsor guidelines.

Regulatory Violations

1. The IRB shall investigate allegations concerning possible non-compliance with these policies and all applicable federal, state, and institutional polices and regulations.
2. During such investigations, confidentiality will be maintained concerning the source of the report to the extent allowed by law.
3. Action taken will include: (a) presentation of the allegation to the person(s) involved with a request for a response; (b) review of the problem by the IRB and communication of its recommendations to the investigator; and (c) presentation to the IRB by the investigator at a full committee meeting, if appropriate.
4. Any instance of serious or continuing investigator non-compliance with federal, state, UCSD or VASDHS regulations or policies will be reported promptly to the UCSD Institutional Official for Human Subjects Protections, the Dean, UCSD School of Medicine, the Office for Protection from Research Risks (OHRP) and the US FDA (for FDA-regulated test articles). Noncompliance by VA investigators will be reported to the VA R&D Committee and, through the VA R&D Committee to the VA ORO in compliance with relevant VA policies.

Applicable Regulations Procedures

[45 CFR 46.112](#)

[45 CFR 46.113](#)

Person(s) Responsible	Procedures
HRPP program staff	Respond to all inquiries and ‘whistleblower’ complaints promptly
IRB	Develop plan for and implement investigation of

Administrator IRB Chairs or designee	alleged noncompliance. Maintain documentary evidence of investigation Report findings to principal investigator, appropriate institutional officials, and outside agencies
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e-IRB electronic submission and review

Policy

The document management logistics of the IRB review and oversight process are a substantial burden to faculty investigators, to the Human Research Protections Program (HRPP) office, and to members of the IRBs who perform the essential task of reviewing proposed projects, amendments, and adverse event reports for their impact on the safety of human research participants. It is not uncommon for the reading materials associated with a single IRB meeting to comprise more than 1000 pages, which is both a challenge in terms of pounds of paper and a navigational challenge for quickly locating pertinent information among hundreds of documents.

The HRPP has undertaken an electronic document submission, distribution and archiving project named the “e-IRB” that uses paperless methods for acquiring documents from investigators, providing them to IRB reviewers, and archiving them in permanent form. These technologies are being developed, deployed and refined with the following goals:

1. To improve the efficiency and reduce the burden of the document review process performed by IRB members
2. To compensate IRB members for their committee work
3. To reduce the burden upon faculty investigators in the submission of materials necessary for IRB review and ongoing oversight of research projects
4. To improve the systematic infrastructure of the HRPP office for creating, archiving and providing access to large numbers of research-related documents
5. To improve the responsiveness of the HRPP office to inquiries and shared oversight issues arising from other organizational units, including research offices of the VA Medical Center, Veterans Medical Research Foundation (VMRF), San Diego Children’s Hospital, and the federal Office of Human Research Protections (OHRP)
6. To improve coordination among related administrative processes such as the School of Medicine clinical trials contracting, Office of Contracts and Grants, campus Conflict of Interest, and Institutional Biosafety/Radiation Safety review committees

The electronic document management systems of the HRPP are based on acquiring and distributing both editable documents (e.g., consent forms in Microsoft Word or WordPerfect format) and non-editable archival forms (e.g., Adobe Portable Document Format PDF page images).

The creation and maintenance of archival documents will be compliant with the electronic signature and access control provisions of 12 CFR 11(c). Certification of system controls and original signatures will be submitted to the FDA Regional Office per the provisions of 21 CFR 11. As new staff members are employed and others depart, updated signature filings will be made to maintain currency of the FDA electronic document registration.

Applicable Regulations Procedures

[21 CFR 11 subpart C](#)

Person(s) Responsible	Procedures
IRB Administrator	Maintain currency of FDA electronic signature documentation.

References Forms and Links

e-IRB services link of IRB website: <http://irb.ucsd.edu>

Radiation Exposure and Radioisotopes

Policy All projects involving radiation exposure will be referred for review by the radiation safety committees of UCSD and VASHDS, as appropriate to the site where the research will be conducted.

If radioisotopes are involved in the proposed project, additional approval for their use in humans is required. If research is to be conducted at the UCSD Medical Center, the Radiation Safety Officer must be contacted by the investigator for instructions (858-534-1069). If the research is to be conducted at the VA Medical Center, the Radiation Safety Office, VA 552-8585 extension 3911 must be contacted.

Radiation Safety Committee (RSC) approval may be obtained before, during, or after application to the IRB. Final IRB approval, however, is contingent upon approval of the appropriate RSC.

Investigators will note on the IRB application face pages the types of radiation sources proposed for use in the study, and provide in the risk/benefit section of the research plan an assessment of the risks of radiation exposure. The research plan will be reviewed by both the RSC and IRB. Each committee will make independent assessments of the risks and benefits of the procedures involving radiation, and no research may be approved without concurrence of the IRB and the RSC. The review documentation provided by the RSC to the IRB will be incorporated into the archival project file.

Interactions between the RSC and IRB are facilitated by a radiation review status field and a radiation review notes field maintained in the IRB project tracking system,. These data can be updated online via a web interface provided to the RSC. The online interface also provides to RSC copies of all correspondence issued by the IRB relevant to a research project.

Applicable Regulations [21 CFR 812.2\(b\)\(1\)\(ii\)](#) [21CFR 56.108\(a\)\(1-2\)45 CFR 46.109](#)
 [21 CFR 812.66](#) [45 CFR 46.111](#)

Procedures	Person(s) Responsible	Procedures
	HRPP staff	Determine the existence of radiation use in protocol submissions, route proposals to the appropriate radiation safety committee to ensure that findings and feedback are provided to investigators

Banking of Specimens

Policy Research involving material that can be linked, directly or indirectly by a code, to personal information concerning the source of the material constitutes research that is subject to federal regulations and IRB approval. Research using unlinked samples also requires IRB review, as the IRB needs to ensure that the process by which the material is rendered unidentifiable is appropriate and secure. Research using human genetic material or genetic testing poses special concerns and always requires IRB review. For VA investigators there may be additional tissue banking review and documentation requirements; the HRPP will coordinate reviews of proposals involving tissue banking by VA investigators with the VA R&D office.

IRB Review Procedures

The Committee will consider the application by means of an expedited or full-committee review process providing that the project meets the criteria for such review. In order to facilitate review of the project, the investigator will set forth the following in the Application for IRB Review:

- 1) a thorough justification of the research design, including a description of procedures used to minimize risk to subjects,
- 2) a full description of the process by which samples will be obtained,
- 3) any plans to obtain access to medical records of the subjects, and
- 4) a full description of the mechanisms that will be used to maximize the protection against inadvertent release of confidential information.

The investigator should address the relevant aspects of these issues in an appropriate manner in the Consent Document.

The principal risk of such research is primarily psychosocial in nature, resulting from the inappropriate release of information to the subject and third parties. The IRB will consider the research to be of minimal risk if:

- 1) the study adequately protects the confidentiality of personally identifiable information, and isolates research results from the subject's general medical records
- 2) the study does not involve the inappropriate release of information

to third parties, including other researchers and institutions, and

- 3) if appropriate, the study design incorporates a plan for whether, when and how to reveal findings to the sources or their physicians, with disclosure to the subject permitted only when all the following apply:
 - a) the findings are scientifically valid and confirmed
 - b) the findings have significant implications for the subject's health concerns, and
 - c) a course of action to ameliorate or treat these concerns is actually available

Expedited review may be permitted if it is determined that the investigator has adequately addressed these issues.

Informed Consent Requirements

Informed consent from the subject is generally required for research involving human biological material. In the case of research involving existent identified or coded samples, it may not be feasible to obtain such consent. If in the original consent document subjects anticipated and agreed to further participation in this way, then additional consent is unnecessary. However, documents may not exist or, when they exist, they do not address the possibility of such research. In such cases, unlinking, or new consent may be necessary to conduct the research, unless a waiver of informed consent is possible.

The IRB may waive the requirement for informed consent if the requirements appropriate. The determination of minimal risk must be made, as described above. In determining whether a waiver of consent would adversely affect the rights and welfare of subjects, the IRB will consider whether:

- 1) the waiver would violate any state or federal statute or customary practice regarding an entitlement to privacy or confidentiality;
- 2) the study will examine traits commonly considered to have political, cultural, or economic significance to the study subjects; and
- 3) the study's results might adversely affect the welfare of the subject's community (if applicable).

If the study poses more than minimal risk and consent cannot practicably be obtained, the removal of identifiers may be required.

In general, a separate informed consent form should be used. In addition to the required and optional elements of informed consent, the informed consent form should contain the following additional elements, if applicable.

- If research results of the reuse of the specimen will this be conveyed to the subject.
- If the subject will be re-contacted after the original study is completed.
- If the subject requests, the specimen and all links to the clinical data will be destroyed.
- That refusal to participate does not affect the subject's ability to participate in any associated therapeutic research.
- If the proposed research study involves the potential for psychosocial harm to the subject's family members, relatives or members of the subject's ethnic group
- If the research has a reasonable likelihood of leading to the development of a commercial product, subjects should be informed that they might not benefit from the product.
- If the investigator has any commercial interest from which he/she may benefit financially, directly or indirectly.
- If the specimen will be used for future research and allow the subject the choice of how the specimen will be used. The consent should provide subjects with a sufficient number of options to help them and fully clarify the present and future uses of their samples. Options might include: a) refusal to use their samples in any research, b) permitting use of their samples only in unidentified or unlinked form, c) permitting coded or identified use of their samples for the present study only, with further contact required to do further studies, d) permitting coded or identified use of their samples for any study relating to the condition for which the sample was originally collected, with further contact allowed to seek permission for other types of studies, e) permitting coded use of their samples for any future study.

Storage and Reuse of Specimens

Human biological material is not considered to be "banked" (stored) if the specimens are used for only the specific purposes defined in the protocol and are destroyed either when the specific use is completed or at the end of the protocol. Specimens collected and stored for future research purposes are considered "banked" specimens. Reuse of specimens must be consistent with the consent under which they were collected, and the

reuse must only occur through an IRB-approved protocol.

If the specimens are sent to an institution outside of UCSD for testing or use as defined in an IRB-approved protocol, a written understanding between the UCSD or VASDHS investigator and the outside institution must specify the use of the specimens as defined in the protocol and that the specimens will be destroyed or returned to the Principal Investigator once the analysis is completed. A copy of this written understanding must be on file before work may commence. This may occur through a Material Transfer Agreement (MTA) of UCSD or VASDHS.

Once the specific analyses are performed the remainder of the specimens must be destroyed or returned to the Principal Investigator for destruction. The remaining quantity may not be retained or stored by the outside institution. If the specimens are destroyed at another institution, that institution must certify in writing to the Principal Investigator the destruction of the specimen.

The investigator storing the banked specimens must retain a copy of the original consent, a record of the use of the specimens, and the protocols under which they were used.

The minimal amount of person-identifiable data necessary should be shared with outside institutions, and use of “de-identified” (in HIPAA parlance) data is preferred in all cases if it meets the scientific objectives of the study. In some cases the IRB may require that a Certificate of Confidentiality be obtained.

If specimens are to be received by UCSD or VASDHS for testing or use, the UCSD or VA investigator must obtain IRB approval or a determination of exemption before the work may begin. In addition, the Principal Investigator must provide a written letter of assurance indicating that samples were collected with appropriate institutional approvals and certifying that confidentiality will be maintained. The outside investigator will provide documentation of IRB approval or documentation of a determination of exemption. Consent forms, or protocols from the outside investigator may also be required. A copy of these documents will be placed in the study file.

**Applicable
Regulations**

[Report and Recommendations of the National Bioethics Advisory Committee, 1999.](#)
[45 CFR 46.110](#)

[VA Directive 2000-043; Banking of Human Research Subjects' Specimens](#)

Procedures

Person(s) Responsible	Procedures
Investigator	Provide necessary information and documentation
Chair, IRB Members	Review the information provided and the informed consent form according to the criteria outlined in Section 703. Ensure that informed consent documents and methods are in compliance with regulations Make assessments as to risks, benefits and the adequacy of subject protections Make recommendations as to the appropriate IRB action

Advertisements and Recruitment Materials

Policy An important issue in human research, especially in the context of clinical trials, is the “therapeutic misconception” associated with new interventions. Clinical studies should be designed with the concept of equipoise, which is that there should be sufficient data to support the notion that in a randomized clinical trial neither arm is a priori known to be superior to the other. In advertising, the concept of “new” is intentionally made synonymous with “improved” but this is antithetical to the scientific principles underpinning human experimentation.

For this reason, the IRB will review the content of all submitted proposed advertisements, proposed recruitment methods, and all other related written material to be provided to subjects. No claims should be made either explicitly or implicitly that the experimental drug or device is safe or effective for the purpose under investigation, or that the drug or device is superior to any other drug or device. This is especially critical when a study may involve subjects who are likely to be vulnerable to undue influence. According to FDA, advertisements should be *limited* to the following:

- Name and address of the clinical investigator
- Purpose of the research and summary of eligibility criteria
- Straightforward and truthful description of the benefits to the subject
- Location of the research and who to contact for information
- All advertisements will be stamped with the IRB name.

Institutional funding vehicles, such as VMRF, may have additional restrictions to be followed.

HRPP maintains an online database for recruitment of study participants that is published as part of the UCSD Healthcare website (<http://health.ucsd.edu>). Study staff associated with approved protocols may create basic project descriptions compliant with the elements listed above by submitting the information to the irb.ucsd.edu website. These project descriptions are reviewed by HRPP staff for accuracy and compliance, edited if needed, and published electronically. This electronic publication constitutes IRB project approval of the submitted recruitment information.

Applicable Regulations

[45 CFR 46.301-306](#)

[21 CFR 56](#)

Procedures	Person(s) Responsible	Procedures
	IRB members HRPP program staff	Review recruitment materials for compliance with applicable policies

References UCSD Healthcare Directory of Clinical Research Studies Seeking
Forms and Volunteers: <http://health.ucsd.edu/ntrials/>
Links

Online submission web pages for new projects:
<http://irb.ucsd.edu/ntrialslogin.shtml>

Section Four: Functions and Operations

IRB meetings

Policy Except when an expedited review process is used, the IRB will review proposed research at convened meetings. The each IRB committee will meet at least monthly, or more often as needed, at a date and frequency determined by the Chair and the IRB Administrator. IRB meetings will be held at locations convenient to the majority of the committee members; whenever feasible, meetings will be held in the HRPP office conference area or other UCSD conference facility with wireless coverage, to take advantage of the wireless network capabilities of the office for access to computerized project tracking, real time MEDLINE and drug database searching, and other Internet-accessible information resources.

A. Meeting Procedures

Prior to the meeting, the IRB professional staff will designate one primary reviewer whose professional interests are in the scientific areas for each research proposal, and one secondary reviewer. The reviewer(s) must be voting members or alternate members who will vote. Physicians and PhD level physical, biological, or social scientists are considered to have primary concerns in the scientific area. Also included in this group are nurses, pharmacists and other biomedical health professionals. Additional reviewers or special consultants may also be designated. In general, two reviewers will be assigned, but for proposals of low risk and/or complexity, the Chair may choose to assign a single reviewer.

A meeting agenda will be prepared by the HRPP program staff and distributed with the meeting materials to IRB members prior to each meeting. A copy of the agenda and attached materials will be maintained on file with the meeting minutes.

A summary of expedited reviews conducted since the previous meeting will be made available to IRB members as a component of the meeting agenda and time will be allotted during the meeting for discussion.

An HRPP staff member will take minutes of each meeting. Minutes will be written in sufficient detail to document the activities of the IRB. Draft minutes will be distributed to members prior to the next IRB meeting. The draft minutes will be discussed at the meeting and corrections requested by the IRB members will be made by the administrator or designee. The minutes will then be committed to final form and made available for

Reviewers (primary and secondary)	Review all relevant meeting materials Prepare IRB meeting presentation (summary, issues and recommendations) Complete reviewer worksheets
IRB Members	Review materials for all projects prior to meeting

Categories of Action

Policy The IRB has the authority to take one of the actions outlined below after reviewing a research proposal. Except when the expedited review process is used, these actions will be taken by a vote of a majority of the regular and alternate members present, except for those members present but unable to vote in accordance with IRB's conflict of interest policies.

A. Categories of Action:

1.	Approval	Action taken if majority of committee votes for approval and no more than one dissenting vote is cast.
2.	Approval Pending	Action taken if the IRB requires minor additional information and/or modifications. The needed revisions are agreed upon at the meeting. The investigator is required to concur and provide written revision of the documents. When revisions are made by the investigator, the IRB Chair or her/his designee(s) approves the revised documents and allows the study to begin.
3.	Deferral:	Action taken if substantial modification is required or if insufficient information is at hand to judge the application adequately (e.g., the risks and benefits cannot be assessed with the information provided). The study is deferred and the investigator is informed of the reason(s) for the action. In order to receive approval for a deferred protocol, it must be submitted for full IRB review at a subsequent, convened meeting. The IRB's determination concerning the subsequent amended submission will be documented in the minutes of that meeting.
iv.	Disapproval:	Action taken if two or more dissenting votes are cast that would not be altered by the proposed modifications.

B. Approval and Continuing Review Dates

IRB approval is effective as of the date of the convened meeting of the

IRB at which the action to approve was taken, indicating that all modifications requested during initial review, if any, have been made. Because investigators may take time to submit modifications or information needed to satisfy the approval pending stipulations, the release date of the approval letter may occur later than the date of the IRB meeting, and both dates will be included in the approval letter. No subjects can be enrolled prior to the IRB approval date. Approval of the VA Research and Development Committee, Biohazard Subcommittee, and other appropriate institutional committees may also be required before the research can actually begin.

The approval period will expire exactly one (1) year from the date of the most recent convened IRB meeting at which the project was reviewed (not 1 year from the approval release date), unless a shorter period is specified by the IRB during its review of the application. If the project was reviewed at several meetings, the date of the last convened meeting at which the project was reviewed will be used. This is the Continuing Review Deadline. Beyond this date, study approval expires and a study cannot continue.

When a project undergoes annual continuing review and is approved for continuation, the new Continuing Review Deadline is set to not greater than one year after the date of the most recent review of the study at a convened IRB meeting. However, OHRP permits the IRB to reapprove the research up to 30 days prior to the continuing Review Deadline and still maintain the same date for the Continuing Review Deadline.

Study modifications are effective as of the date of signature of the approval memo by the IRB Chair after either expedited or full committee review.

D. Approval and Documentation

The IRB will document that the criteria for approval of the project and the informed consent documents have been discussed at the meeting and that the criteria have been met. This will be documented in the meeting minutes, reviewer worksheets, and other sources. The results of IRB review and actions taken by the IRB will be communicated to the investigator, and to other offices such as the VA R&D Committee where appropriate, in a timely manner.

Applicable Regulations

[21 CFR 56.110\(b\)](#)
[21 CFR 56.111](#)

[38 CFR 16.111](#)
[ICH 3.1.1](#)

Procedures

Person(s) Responsible	Procedures
IRB Administrator	Document all member votes (for, against, abstaining) in the minutes. Summarize relevant discussions in the minutes, in particular, decisions to disapprove or to modify the research. Summarize in detail, all controverted discussions and their resolution.
IRB Chair	Conduct voting process for each submission. Review submitted changes for completeness and complete approval by Expedited review process.

Protocol Audits

Policy The IRB has the authority to observe, or have a third party observe, the consent process and the research it has approved, and to verify that the study is being conducted as required by the IRB. When the IRB opts to assess the conduct of the study or the consent process as part of providing adequate oversight, an audit is conducted by the IRB Chair, a member of the IRB, a member of another IRB or an unaffiliated party. An audit may be study-oriented (focused on a specific study) or investigator-oriented (focused on all the studies of a particular investigator). An audit may be also be classified as routine (part of the normal oversight process) or “for cause”. A “for cause” audit may be initiated in response to any of the following findings:

- an allegation of or evidence suggesting noncompliance with applicable regulations or institutional policies
- noncompliance with policies of the IRB as outlined in this document
- ongoing research is identified which has not been approved by the IRB
- expressed concerns by the sponsor regarding the investigator’s work
- a complaint by a subject in a study about protocol or subject's rights violations
- a potential high risk to subjects
- recruitment of vulnerable populations
- studies that involve large numbers of subjects
- investigators who are conducting multiple studies under IRB jurisdiction
- research by an investigator outside of their specialty areas
- safety or effectiveness findings that are inconsistent with those of other investigators studying the same test article
- too many subjects with a specific disease given the locale of the investigation are claimed
- laboratory results that are outside the range of expected biological variation
- studies selected at the discretion of the IRB
- an allegation of or evidence suggesting abuse of research subjects
- an allegation of or evidence suggesting scientific misconduct

A. Audit Procedures

In order to determine the facts surrounding the conduct of the study, the auditor may review the protocol and any modifications, Investigational Drug Brochure, the informed consent, the investigator’s and the IRB files, subject’s medical and/or research records, case report forms, literature and other documents that could serve to provide factual information regarding the conduct of the study. Although not generally recommended, the auditor may conduct interviews with the Investigator, members of the study team, or research subjects. A written report of findings will be provided to the IRB for further review. If the audit report documents substantial issues of noncompliance, the IRB may take action as outlined in the section on Sanctions and Disciplinary Actions.

B. Third Party Verification

Third party verification of information provided by an Investigator may be necessary to ensure protection of subjects. The IRB may require verification of any information provided by an investigator as part of an initial application or as part of a re-approval, interim or completion report. The IRB also has the authority to observe, or have a third party observe, the consent process and the research it has approved. The need to verify any information, the information that needs verification and the extent to which the information will be verified will be determined by the IRB at a convened meeting. Methods of third party verification include:

- 1) Direct observation of research procedures by an IRB member
- 2) Direct request to sponsor for information
- 3) Direct request to Data Safety Monitoring Board (DSMB) for information

Applicable Regulations	45 CFR 46.103 (b)(4)(ii)	21 CFR 56.108(a)(2)
	38 CFR 16.109(e)	21 CFR 56.109 (f)
	38 CFR 16.103(b) (4)(ii)	45 CFR 46.109(e)
Procedures	VHA Handbook 1200.5	
	Person(s) Responsible	Procedures

<p>IRB Administrator</p>	<p>Provide auditor with a copy of the protocol and any modifications, Investigational drug brochure, informed consent, IRB files and any other documents that could provide factual information regarding the conduct of the study.</p> <p>Provide audit with Audit Checklist</p> <p>Contact Investigator to arrange audit logistics.</p>
<p>Auditors</p>	<p>Review all documents that could provide factual information regarding conduct of the study.</p> <p>Confirm that the study is being conducted in compliance with the documents provided, by observation if possible, especially: a) methods of subject recruitment, and or safeguards for subjects vulnerable to coercion or undue influence; b) process for obtaining informed consent; c) version of informed consent used; d) facilities available in an emergency; e) adherence to inclusion/exclusion criteria.</p> <p>Confirm information about any adverse events that may have been reported.</p> <p>Obtain information about any adverse events that may not have been reported.</p> <p>Confirm status of project (enrolling, inactive etc)</p> <p>Complete Audit Report within 10 working days of completing the audit.</p>
<p>IRB Members</p>	<p>Review Audit Report</p> <p>Assess the need for additional information.</p> <p>Determine audit conclusion.</p> <p>Vote on remedial action imposed on investigator, as necessary.</p>

References UCSD On Site Audit Checklist
Forms and FDA GCP Audit Guidelines
Links

Communications, Sanctions, Appeals and Disciplinary Actions

Policy The mandate of the IRB and its authority to require changes in research procedures developed by investigators has the potential to generate adversarial reactions and negative responses. It is the policy of this program that all communications by HRRP staff to and about faculty, staff, students, and their research activities will be conducted in a respectful and courteous manner.

The IRB has the authority to suspend or terminate protocols that are found to be non-compliant with institutional policies and procedures, state laws, and/or federal laws or regulations or have been associated with unexpected serious harm to subjects.

A. Regulatory Noncompliance

Potential occurrences of regulatory noncompliance in research may be revealed by a complainant or through formal and informal monitoring activities. The Chair or his/her designee will initially review allegations of noncompliance and determine whether the alleged practices appear to (1) cause injury or any other anticipated problems involving risks to subjects or others or (2) constitute serious or continuing noncompliance with IRB regulations. The Chair may initiate further investigation or other measures as necessary to protect the safety of research subjects.

- 1) **Minor Noncompliance:** Minor occurrences are those where it can be determined that the investigator unintentionally missed or omitted a requirement defined by the IRB that has not affected subject safety. If a minor occurrence is found, the Administrator and/or Chair will notify the investigator of the error and define corrective action that needs to be taken. The Administrator will maintain documentation of any telephone or written communications. The Administrator and/or Chair will confirm that corrective action has been taken.

Whenever possible, investigators will be assisted to achieve compliance without the need for sanctions. However, if the investigator fails to cooperate with the IRB requests to correct minor noncompliance, this inaction will be treated as serious noncompliance.

- 2) **Serious Noncompliance:** Serious violations are those where the investigator was non-compliant with his/her federally regulated responsibilities as an investigator, placing a subject at increased risk of

injury. Failure to take corrective action of a minor instance of noncompliance after being notified by the IRB may also be considered a serious violation. When suspected serious violations are brought to attention, the Chair may temporarily suspend active enrollment of subjects and/or remove ongoing subjects from the study pending a timely investigation and review by the full IRB.

Depending upon the situation, a study or investigator audit may be initiated by the IRB or the Chair, per procedures outlined in the section on Protocol Audits. The IRB or the Chair may temporarily suspend approval of research at any time during this process.

The IRB will review the audit report to determine whether a serious violation has occurred or whether the investigator has engaged in a pattern of disregard for research regulations, policies or procedures. The review may be performed by the full IRB, or by a subcommittee of IRB members selected by the Chair, which then reports to the full IRB. However, the final determinations and actions will be made by the full IRB at a convened meeting.

Upon completion of the review, the IRB may dismiss the allegations, confirm that compliance was achieved with the cooperation of the investigator, establish a plan for corrective action, impose or recommend sanctions, report to appropriate federal agencies, and/or recommend investigation for scientific misconduct.

Whenever possible, technical assistance will be recommended to investigators to assist them with achieving compliance without the need for imposition of sanctions. However, in cases where cooperation does not occur, or when it is determined that the safety or welfare of subjects or the integrity of the institution are or have been placed at risk, sanctions may be imposed.

Sanctions that may be imposed by the IRB include, but are not limited to: a) suspension or termination of project(s); b) more frequent review of project(s); c) compliance audits; d) letters of censure; e) restrictions on serving as an investigator on human subjects protocols; f) research privilege probation; g) suspension or termination of research privileges; h) requiring additional education and training of the investigator or their research staff; i) embargo or retraction of publications, j) reporting of noncompliant activities to governmental entities; k) or reclassification as possible scientific misconduct.

Additional sanctions beyond the authority of the IRB may be recommended in writing to the Department Chair, the Dean of the

school within which the research activity took place, the UCSD Vice Chancellor for Research, the VASDHS, VMRF, or other appropriate authorities.

The IRB will promptly report any suspension or termination of IRB approval for research and serious instances of noncompliance to appropriate Federal sponsoring agencies, OHRP, and the institution employing the investigator.

If the IRB determines that an investigator may continue his/her project with corrective action, or approval is reinstated after appropriate corrective action, a plan for continuing review will be formulated. Continuing review in this situation may include, but is not limited to audits, Interim Reports, and third party verification. This will be carried out on a periodic basis until the IRB is satisfied that the problem has been adequately resolved. The Investigator will be invited to respond in writing to the results of the review.

B. Notification and Documentation

If the IRB has determined that serious noncompliance has occurred, or that a study must be suspended or terminated, the investigator will be notified by telephone within 24 hours of the decision and in writing within 3 working days. In all other cases, the results of IRB Review will be communicated in writing within 5 working days. A response from the investigator specifying corrective actions will be required within 10 working days of notification. The response should include a formal corrective action plan, the actions to be taken, responsibility, and when the actions will be effective. Where appropriate, the study sponsor and appropriate state and federal authorities will also be notified in writing of the action being taken by the IRB.

C. Scientific Misconduct

If at any time during the investigation the IRB or Chair finds evidence to suggest the possibility of scientific misconduct, the matter will be referred to the Dean for Academic Affairs and to the VA ACOS for Research, to pursue according to institutional and University policies.

D. Appeals

Investigators who wish to appeal a sanction imposed by the IRB may contact the Research committee of the UCSD Academic Senate. The Academic Senate may, upon review of the issues involved, initiate an inquiry into the process and evidence used by the IRB to arrive at its

decision, and issue an opinion on the appropriateness of that process and evidence. In compliance with 45 CFR 46.112, the Academic Senate may not override an IRB decision to disapprove a research project involving human subjects.

Applicable Regulations [21 CFR 56.113](#)
 [45 CFR 46.113](#)

[VHA Handbook 1200.5](#)
[38 CFR 16.113](#)

Procedures	Person(s) Responsible	Procedures
	IRB Administrator	Notify investigators of minor instances of noncompliance Prepare correspondence to investigators and distribute to relevant parties as required.
	IRB Chair	Make an initial evaluation and initiate suspension or further action as needed
	IRB Members	Review files and make determination whether serious noncompliance has occurred. Determine if harm to subjects has occurred, and suspend or terminate study as needed. Determine plan of corrective action, sanctions, and monitoring plan as needed.

Appendix

Abbreviations

ADE	Adverse Drug Event/Experience
AE	Adverse Event
CFR	Code of Federal Regulations
COI	Conflict of Interest
CTA	Clinical Trial Agreement
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organizations
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HRPP	UCSD Human Research Protections Program
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IND	Investigational New Drug
IRB	Institutional Review Board
MTA	Materials Transfer Agreement
OCGA	Office of Contract and Grant Administration
OHRP	Office for Human Research Protections
ORO	Office of Research Oversight
PHS	Public Health Service
PI	Principal Investigator
R&D	Research & Development
SAE	Serious Adverse Event
SOM	School of Medicine
SOPP	Standard Operating Policies and Procedures
UCSD	University of California, San Diego
VASDHS	Veteran Affairs, San Diego Healthcare System
VMRF	Veterans Medical Research Foundation

Definitions

Act means the Federal Food, Drug, and Cosmetic Act, as amended (21 CFR)

Adverse Drug Reaction (ADR): In the pre-approval clinical experience with an experimental, investigational (new) medicinal product or its new usages, particularly as the therapeutic dose(s) may not be established: all noxious and unintended responses to a medicinal product related to any dose should be considered adverse drug reactions. The phrase "responses to a medicinal product" means that a causal relationship between the medicinal product and an adverse event is at least a reasonable possibility (for example, the relationship cannot be ruled out.) Regarding marketed medicinal products: a response to a drug which is noxious and unintended and which occurs at doses normally used in man for prophylaxis, diagnosis or therapy of diseases or for modification of physiological function. (ICH 1.1)

Adverse Event (AE): Any untoward medical occurrence in a patient or research subject administered a pharmaceutical product or other research intervention and that does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product or research procedure, whether or not related to the medicinal (investigational) product or procedure. (ICH 1.2)

Approval Date: The IRB Approval Date is the date that the IRB approval memo for a project is signed as approved by the IRB Chair or his/her designee.

Approved Off-Site Location: A research site outside of the UCSD facilities, VA medical center or approved VA-leased space which has been approved for the conduct of VA-funded research through an off-site waiver as described in VA Handbook 1200.16.

Associated with the use of the drug: There is a reasonable possibility that the experience may have been caused by the drug (21 CFR 312.32).

Audit: A systematic and independent examination of trial-related activities and documents to determine whether the evaluated trial-related activities were conducted, and the data were recorded, analyzed, and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), good clinical practice (GCP), and the applicable regulatory requirement(s) (ICH 1.6).

Clinical Trial: Any experiment that involves a test article and one or more human subjects and that either is subject to requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the act, or is not subject to requirements for prior submission to the Food and Drug Administration under these sections of the act, but the results of which are intended to be submitted later to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The term does not include experiments that are subject to the provisions of 21 CFR 58, regarding nonclinical laboratory studies. The terms clinical study, clinical trial, and clinical investigation are deemed to be synonymous for purposes of this Manual.

Coded Sample: A coded sample is one that is associated with a code that could permit an agent of the repository to link it with the subject. Even though the investigator may not be able to directly link the sample with a subject, research using such samples is subject to IRB review.

Confidentiality: Prevention of disclosure, to other than authorized individuals, of a sponsor's proprietary information or of a subject's identity. (ICH 1.16)

Conflict of Interest: A convergence of an investigator's private interests with his or her research interests, such that an independent observer might reasonably question whether the investigator's professional actions or decisions are improperly influenced by considerations of personal financial gain.

Continuing Review Deadline: The Continuing Review Deadline is exactly one year after the date of the most recent review of the study at a convened IRB meeting, or shorter if required by the IRB. Beyond this date, study approval expires and a study cannot continue.

Department or Agency Head: The head of any Federal Department or Agency and any other officer or employee of any Department or Agency to whom authority has been delegated. (38 CFR, 45 CFR).

Direct Access: Permission to examine, analyze, verify, and reproduce any records and reports that are important to evaluation of a clinical trial. Any party (e.g., domestic and foreign regulatory authorities, sponsors, monitors, and auditors) with direct access should take all reasonable precautions within the constraints of the applicable regulatory requirement(s) to maintain the confidentiality of subjects' identities and sponsor's proprietary information (ICH1.21).

Disability: A substantial disruption of a person's ability to conduct normal life functions (21 CFR 312.32).

Documentation: All records, in any form (including, but not limited to, written, electronic, magnetic, and optical records; and scans, x-rays, and electrocardiograms) that describe or record the methods, conduct, and/or results of a trial, the factors affecting a trial, and the actions taken. (ICH 1.22)

Emergency use means the use of a test article on a human subject 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.

Exculpatory: To clear from a charge of fraud or guilt.

Family member: Any one of the following legally competent persons: spouse; parents; children (including adopted children); brothers, sisters, and spouses of brothers and sisters; and any individual related by blood or affinity whose close association with the subject is the equivalent of a family relationship. (21 CFR)

Good Clinical Practice (GCP): A standard for the design, conduct, performance, monitoring, auditing, recording, analyses, and reporting of clinical trials that provides assurance that the data and reported results are credible and accurate, and that the rights, integrity, and confidentiality of trial subjects are protected. (ICH 1.24)

Human Biological Material: Any material derived from human subjects, such as blood, urine, tissues, organs, hair, nail clippings, genetic material, or any other cells or fluids, whether collected for research purposes or as residual specimens from diagnostic, therapeutic or surgical procedures.

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

Human subject: A living individual about whom an investigator (whether professional or student) conducting research obtains: 1] data through intervention or interaction with the individual or 2] identifiable private information. The individual may be a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. (21 CFR, 38 CFR, 45 CFR). The definition of human subject provided in the Federal Policy is expanded to include investigators, technicians, and other assisting investigators, when they serve in a "subject" role by being observed, manipulated or sampled.

Human subjects research: Research involving one or more human subject, as they are defined here. This definition includes all clinical trials, as defined above, as well as all other types of research involving human subjects.

Identified sample: A sample that is associated with a personal identifier such that the researcher could directly link it with a subject. Research involving this sample is subject to IRB review and approval.

Impartial witness: A person, who is independent of the trial, who cannot be unfairly influenced by people involved with the trial, who attends the informed consent process if the subject or the subject's legally acceptable representative cannot read, and who reads the informed consent form and any other written information supplied to the subject. (ICH 1.26)

Informed Consent: A process by which a subject or their legally authorized representative voluntarily confirms his or her willingness to participate in a particular trial, after having been informed of all aspects of the trial that are relevant to the subject's decision to participate. Informed consent is documented by means of a written, signed, and dated informed consent form (ICH 1.28).

Institutional Review Board (IRB): Any board, committee, or other group formally designated by an institution to review biomedical research involving human subjects, to approve the initiation of, and to conduct continuing review of such research (21 CFR, 38 CFR, 45 CFR). An independent body constituted of medical, scientific, and nonscientific members, whose responsibility it is to ensure the protection of the rights, safety, and well-being of human subjects involved in a trial by, among other things, reviewing, approving, and providing continuing review of trials, of protocols and amendments, and of the methods and material to be used in obtaining and documenting informed consent of the trial subjects (ICH 1.31).

Interaction: Includes communication or interpersonal contact between investigator or his/her designee and subject (38 CFR, 45 CFR).

Intervention: Both physical procedures by which data are gathered (for example, venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes (38 CFR, 45 CFR).

IRB approval: The determination of the IRB that the human subjects research has been reviewed and may be conducted at an institution within the constraints set forth by the IRB and by other institutional and Federal requirements.

Investigational Product: A pharmaceutical form of an active ingredient, device or placebo being tested or used as a reference in a clinical trial, including a product with a marketing authorization when used or assembled (formulated or packaged) in a way different from the approved form, or when used for an unapproved indication, or when used to gain further information about an approved use (ICH 1.33)

Investigator: An individual who actually conducts human subjects research, i.e., under whose immediate direction the test article or research procedure is administered or performed upon, a subject, or, in the event of an investigation conducted by a team of individuals, is the responsible leader of that team (21 CFR).

Investigator's Brochure (IB): A compilation of the clinical and nonclinical data on the investigational product(s), which is relevant to the study of the investigational product(s) in human subjects. (ICH 1.36). This document is also known as an Investigational Drug Brochure.

Legally Authorized Representative: An individual or judicial or other body authorized under applicable law to consent on behalf of a prospective subject to the subject's participation in the procedure(s) involved in the research (21 CFR, 38 CFR, 45 CFR). In the State of California, "legally authorized representative" includes only persons appointed as healthcare agents under Durable Powers of Attorney for Health Care (DPHAC) and court appointed conservators of the person.

Life-threatening adverse drug experience: Any adverse drug experience that places the patient, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death (21 CFR 312.32)

Linked sample: A sample associated with a personal identifier or a code that allows it to be linked with a subject, even if the investigator may not be able to directly link the sample with a subject. Research using such samples is subject to IRB review.

Minimal risk: The probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (21 CFR 56.102, 45 CFR 46.102(i), 38 CFR)

Private Information: Includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, medical record). Private information must be individually identifiable (i.e., the identity of the of the subject is or may be readily ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects (38 CFR, 45 CFR).

Protocol: A document that describes the objective(s), design, methodology, statistical considerations, and organization of a trial. The protocol usually also gives the background and rationale for the trial, but these could be provided in other protocol referenced documents (ICH 1.44)

Protocol Amendment: A written description of a change(s) to or formal clarification of a protocol (ICH 1.45).

Randomization: The process of assigning trial subjects to treatment or control groups using an element of chance to determine the assignments in order to reduce bias (ICH 1.48).

Regulatory Noncompliance: Failure to adhere to institutional policies and procedures, state laws, federal laws or other regulations governing the conduct of human subjects research. This includes such acts as failure to obtain or maintain approval for research or to adhere to an approved protocol, failure to obtain informed consent when required, coercion of human subjects, performance of an unapproved procedure, performance of research at an unapproved site, or failure to file protocol modifications, applications for study reapproval, and adverse event reports.

Research: A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalized knowledge. Activities that meet this definition constitute research for the purposes of this Manual, whether or not they are conducted or supported under a program that is considered research for some other purposes. For example, some demonstration and service programs may include research activities (38 CFR, 45 CFR).

Scientific Misconduct: Serious deviation from accepted practice in carrying out research or in reporting the results of research, or material failure to comply with Federal requirements affecting specific aspects of the conduct of research, such as the protection of human subjects. This may include plagiarism, misrepresentation of authorship, fabrication falsification or destruction of data, or other serious deviations from accepted scientific practices, such as obstruction of another's research, violation of confidentiality, intentional deception, omission, research dishonesty, or repeated incidents of regulatory noncompliance. (VHA Handbook 1200.5)

Serious Adverse Event (SAE) or Serious Adverse Drug Reaction (Serious ADR): An AE or ADR occurring in a patient or subject enrolled in a research study is serious if it results in any of the following outcomes: death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or is a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization, may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalizations, or the development of drug dependency or drug abuse (21 CFR 312. 32).

Source Documents: Original documents, data, and records (e.g., hospital records, clinical and office charts, laboratory notes, memoranda, subjects' diaries or evaluation checklists, pharmacy dispensing records, recorded data from automated instruments, copies or transcriptions certified after verification as being accurate and complete, microfiches, photographic negatives, microfilm or magnetic media, x-rays, subject files, and records kept at the pharmacy, at the laboratories, and at medical or technical departments involved in the clinical trial)(ICH 1.52)

Sponsor: A person or other entity that initiates human subjects research, but that does not actually conduct the investigation, i.e., the test article is administered or dispensed to, or used involving, a subject under the immediate direction of another individual. A corporation or agency that uses one or more of its own employees to conduct an investigation that it has initiated is considered to be a sponsor (not a sponsor-investigator), and the employees are considered to be investigators (21 CFR)

Sponsor-investigator: An individual who both initiates and actually conducts, alone or with others, human subjects research, i.e., under whose immediate direction the test article is administered or dispensed to, or used involving, a subject. The term does not include a corporation or agency. The obligations of a sponsor-investigator under FDA regulations include both those of a sponsor and those of an investigator. (21 CFR)

Standard Operating Policy and Procedures (SOPPs): Detailed, written instructions to achieve uniformity of the performance of a specific function (ICH 1.55).

Subinvestigator: Any individual member of the clinical trial team designated and supervised by the investigator at a trial site to perform critical trial-related procedures and/or to make important trial-related decisions (e.g., associates, residents, research fellows) (ICH 1.56).

Test article: Any drug (including a 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 and 354-360F of the Public Health Service Act (21 CFR)

Unexpected adverse drug experience: Any adverse experience the specificity or severity of which is not consistent with the current Investigator Brochure, or if an Investigator Brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected" as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product (21 CFR 312.32).

Unidentified Sample: An anonymous or unidentified sample is one supplied to the researcher from a repository that has a collection of unidentified human specimens. There is no possibility of linking such samples to the individual. This differs from samples that have been "anonymized" or unlinked by removal of identifiers (see Unlinked Sample).

Unlinked Sample: A biological sample that lacks any identifier or code that may link the sample to an individual. An investigator must differentiate between an unlinked sample that is provided to him by a third party and a sample under the investigator's control from which the investigator proposes to remove any identifying material (“anonymize”) for the purposes of research.

Vulnerable subjects: Individuals whose willingness to volunteer in a clinical trial may be unduly influenced by the expectation, whether justified or not, of benefits associated with participation, or of a retaliatory response from senior members of a hierarchy in case of refusal to participate. Examples are members of a group with a hierarchical structure, such as medical, pharmacy, dental, and nursing students, subordinate hospital and laboratory personnel, employees of the pharmaceutical industry, members of the armed forces, and persons kept in detention. Other vulnerable subjects include patients with incurable diseases, persons in nursing homes, unemployed or impoverished persons, patients in emergency situations, ethnic minority groups, homeless persons, nomads, refugees, minors, and those incapable of giving consent. (ICH 1.61) Mentally disabled individuals are a vulnerable population.

Well-being (of the trial subjects): The physical and mental integrity of the subjects participating in a clinical trial (ICH 1.62).

Change Summary

3/29/2004 changes relative to version date 1/21/2004

1. Added section on institutional policy regarding exempt categories of research described in 45 CFR 46.101(b), noting that the institution does not recognize these exemptions and research defined in these categories is subject to IRB review by expedited review procedures.
2. Replaced references to VHA Manual M-3, Part 1, Chapter 9 with references to VHA Handbook 1200.5, throughout document.
3. Program Organization text amended to clarify that references to VASDHS also include research administered by its associated research foundation, the Veterans Medical Research Foundation (VMRF).
4. At the request of VASDHS, Appointment, Compensation and Responsibilities section amended to remove requirement that at least one IRB chair have a VA appointment and at least one member of each IRB committee be a member of the VA R&D committee.
5. Informed consent section revised to note that a copy of the consent form (rather than the original) must be placed in the patient's VA medical record.
6. Added additional reporting requirements of VASDHS for adverse events occurring on VA research studies.

5/28/2004 changes relative to version date 3/29/2004

1. Added clarification on page 16 of process for identifying the need for internal and external consultants during IRB review, and need for consultants to submit comments in writing.
2. Clarification on page 27 of the range of items made available to IRB committee members for project reviews.
3. Clarification of qualifications of designated IRB members for performing expedited review.
4. Clarification on page 91 that unanticipated problems will not only be reported to external agencies, but that the IRB may require that all study participants be informed, and if appropriate, re-consented.
5. Clarification on page 15 that one at least one VA IRB member must be present during the review of VA research.
6. Clarification on page 90 that any amendments made by an investigator to a protocol to eliminate an apparent immediate hazard must be promptly reported to and reviewed by the IRB.
7. All references to ORCA changed to ORO due to VA reorganization and renaming of its research oversight operations.
8. Clarification on page 84 regarding reminders sent to researchers regarding project expiration deadlines, and procedures for managing lapsed IRB approvals.
9. Clarification on page 11 that access to records will be monitored by both physical and electronic means, including audit trails of specific projects viewed or copied.
10. Clarification on page 40 of the qualifications to administer informed consent.

