

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

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## **1. General Administration**

### **1.1. Responsibility and Authority**

#### **1.1.1. 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:

- 1) approve, require modifications to secure approval, and disapprove approve 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;
- 2) review, accept, or not accept reports, including adverse events, and require modifications to research protocols;
- 3) to require applications for study re-approval from investigators;
- 4) to oversee conduct of the study;
- 5) to suspend or terminate a study; and
- 6) 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.

#### 1.1.2. Applicable Regulations

[The Belmont Report](#)

[38 CFR 16.101](#)

[38 CFR 16.109\(a,e\)](#)

[38 CFR 16.113](#)

[45 CFR 46.101](#)

[45 CFR 46.109\(a, e\)](#)

[45 CFR 46.113](#)

[21 CFR 50.20](#)

[VHA Handbook 1200.5](#)

[21 CFR 56.109\(a, f\)](#)

[21 CFR 312.34](#)

[21 CFR 312.35](#)

[21 CFR 312.80 to 88](#)

[21 CFR 56.112](#)

[California Health and Safety Code](#)

[24170-24179.5](#)

[21 CFR 56.113](#)

### 1.1.3. Procedures

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

### 1.1.4. References Forms and Links

Federalwide Assurance FWA0004495, available from HRPP office

## **1.2. HRPP Program Organization**

### 1.2.1. Policy

The Dean’s Office, UCSD School of Medicine, supports the UCSD Human Research Protections Program and for personnel and fiscal purposes is an administrative unit of the School of Medicine. The San Diego Veterans Medical Research Foundation (VMRF), and general campus also provide support for the program. 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 nor 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.

A Director who oversees program operations and also functions as the IRB Administrator of record leads the UCSD HRPP. 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.

1.2.2. Applicable Regulations

[38 CFR 16.101](#)  
[38 CFR 16.109\(a,e\)](#)

[38 CFR 16.113](#)  
[45 CFR 46.101](#)

1.2.3. Procedures

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

### 1.3. Review and Updating of SOPP

#### 1.3.1. 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>.

#### 1.3.2. Applicable Regulations

38 CFR 16.104 (b) (4)  
[38 CFR 16.108\(a\)](#)  
[38 CFR 16.115 \(6\)](#)  
[45 CFR 46.103 \(b\) \(4\)](#)

[45 CFR 46.108 \(a\)](#)  
[45 CFR 46.115 \(6\)](#)  
[21 CFR 56.108\(a\)](#)  
[21 CFR 56.115 \(6\)](#)  
[VHA Handbook 1200.5](#)

#### 1.3.3. 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.

## 1.4. Documentation and Records Retention

### 1.4.1. 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 re-approval, study progress reports and interim reports, modifications, adverse event report forms submitted by investigators, and other reports (such as case histories if requested) submitted to the studies. The aforementioned constitute the definition of a “research record”.
- 2) Minutes of IRB meetings in sufficient detail to show the following:
  - a. The presence of a quorum throughout the meeting including the presence of one member whose primary concern is in a non-scientific area;
  - b. Attendance at the meetings including those members who are participating through video or teleconference;
  - c. Alternate members attending the meeting and members participating by video or teleconference have received and reviewed all required information;
  - d. The approval of previous meeting minutes;
  - e. Discussion of expedited reviews and determinations;
  - f. Actions taken by the IRB;
  - g. The vote on actions including the number of members voting for, against, and abstaining;
  - h. That the informed consent document was reviewed in accordance with applicable criteria and contains all of the required elements;
  - i. The justification for waiving any or all of the required elements of informed consent;
  - j. A determination of risk level of investigational devices;
  - k. The names of IRB members who left the meeting because of a real or potential conflict of interest with the proposal under consideration and the reason for the conflict of interest. The minutes will also state that the IRB member was absent from the meeting room for the discussion and voting (and that the quorum was maintained). Minutes must document the fact that a conflict of interest was the reason for the absence.
  - l. The basis for requiring changes in or disapproving research;
  - m. A written summary of the discussion of controverted issues and their resolution;
  - n. Review of additional safeguards to protect vulnerable populations if entered as study subjects; and
  - o. The frequency of continuing review of each proposal as determined by the IRB.

- p. Any significant protocol-specific finding that may alter risk/benefit ratio
  - q. Decisions regarding privacy including use or disclosure of protected health information, including HIPAA decisions
  - r. Any significant new finding provided to participant, if reviewed by committee;
  - s. Many DHHS multi-site studies such as cooperative oncology trials, cardiology trials, and behavioral studies, include a consent document that has been approved by DHHS. The approved consent document must include all information concerning risks or alternative procedures contained in the DHHS-approved sample consent document, unless the IRB has justified in the minutes any deletion or substantive modification of that information.
- 3) Copies of draft minutes available to regulatory agencies, VA R&D, and members of internal and external audit teams as requested for reviewing Committee deliberations and decisions regarding UPRs. Committee minutes will be prepared, reviewed, and approved in a timely manner. Minutes will be available as draft within three weeks of the meeting date. Once approved by the IRB, minutes may not be altered by anyone including a higher authority once approved by the members at a subsequent IRB meeting. Once the final minutes are approved they shall supercede the draft minutes and copies of the draft minutes shall be destroyed and not kept in the ordinary course of business.
  - 4) Copies of all logs, audit reports, expedited reviews and continuing review activities, as appropriate.
  - 5) Copies of all correspondence between the IRB and the investigators.
  - 6) 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).
  - 7) Copies of the Standard Operating Policies and Procedures Manual.
  - 8) Statements of significant new findings provided to subjects.
  - 9) Reports of any complaints received by subjects.
  - 10) Access to current conflict of interest statements from IRB members.
  - 11) Training for IRB members and staff.
  - 12) Informed consent document(s)
  - 13) HIPAA authorization forms

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 (five years for VA studies) 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 (VA R&D Committee), 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.

1.4.2 Applicable Regulations

- |  |   |
|--|---|
| <a href="#">21 CFR 56.103(a)</a>       | <a href="#">38 CFR 16.103 (b)(4-5)</a>      |
| <a href="#">21 CFR 56.108(a-b)</a>     | <a href="#">38 CFR 16.115</a>               |
| <a href="#">45 CFR 46.108 (a)</a>      | <a href="#">ICH 3.2.2</a>                   |
| <a href="#">45 CFR 46.103 (b)(4-5)</a> | <a href="#">21 CFR 56.115</a>               |
| <a href="#">45 CFR 46.115</a>          | <a href="#">VHA Record Control Schedule</a> |
| <a href="#">38 CFR 16.108 (a)</a>      | <a href="#">10-1</a>                        |
|  | <a href="#">VHA Handbook 1200.5</a>         |

1.4.3 Procedures

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

#### 1.4.4 References, Forms and Links

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

### **1.5 UCSD Institutional Policies**

#### 1.5.1 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.

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.

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.

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 Clinical Trials Administrative Services (CTAS), or the Veterans Medical Research Foundation.

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.

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.

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."

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."

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.

### 1.5.2 Applicable Regulations

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

### 1.5.3 Procedures

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

## **2. IRB Organization**

### **2.1. Composition of IRBs**

#### 2.1.1. 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 quorum, defined as attendance of the majority of the members listed on the roster, must be present in order to hold a convened IRB meeting. If at any time during a convened meeting a quorum is lost, the IRBs cannot vote on actions until the quorum is restored. Members present by conference or video-phone who can hear and be heard may be counted as present in meeting quorum requirements.

#### 2.1.1.1. Regular Members

There will be at least one member in attendance 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. A licensed physician, who is a voting member, must be present for research involving an FDA-regulated article.

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. Each IRB membership roster must include sufficient information about member's expertise to permit verification that there is appropriate representation at the meeting for each protocol under review. This includes ensuring that at least one person who is knowledgeable about or experienced in working with a specific field or vulnerable population, for instance, will present at a meeting where such protocols are reviewed.

The Director and Deputy 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 submit reviews for at least 10 of 12 monthly meetings.

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 Vice-Chair will lead the IRB meeting. In the event that the Vice-Chair is unavailable as well, the Chair or Vice-Chair will designate another regular IRB member to chair the meeting.

#### 2.1.1.2. 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.

#### 2.1.1.3. 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.

Special consultants may be used for all aspects of IRB review as determined by the Chair or his/her designee including initial review, amendments, adverse event reports, safety monitoring reports, responses to committee, and continuing review. The Chair is obligated to ask consultants about conflict of interest. Any consultant would be considered to have a conflict of interest if he or she is listed as a collaborator on the

project, received financial compensations from the sponsor for any reason, or meets the Institutional definition for conflict of interest. When a consultant self-identifies conflict of interest a conflicting interest, this conflict must be disclosed to the IRB members reviewing the research and the consultant may not participate in the review.

2.1.2. Applicable Regulations

- |  |  |
|--|--|
| <a href="#">21 CFR 56.107 (a-d, f)</a>         | <a href="#">38 CFR 16.107 (a-d, f)</a> |
| <a href="#">21 CFR 56.115 (a)(5)</a>           | <a href="#">38 CFR 16.103 (b)</a>      |
| <a href="#">45 CFR 46.107 (a-d, f)</a>         | <a href="#">38 CFR 16.115 (a)</a>      |
| 2.1.2.<br><a href="#">45 CFR 46.115(a) (5)</a> | <a href="#">ICH3.2.1</a>               |
| <a href="#">45 CFR 46.103 (b) (3)</a>          | <a href="#">ICH3.2.6</a>               |
| 2.1.3.   | <a href="#">VHA Handbook 1200.5</a>    |

2.1.4.

2.1.3. Procedures

Characteristics of members, including appointment term, committee assignment, departmental affiliation, and professional expertise, are maintained in the HRPP database system. In addition, CVs for members are maintained in binders in the HRPP office available for review by the appropriate authorities. The same process will be followed for pre-identified consultants.

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

## **2.2. Member Appointment, Compensation and Responsibilities**

### **2.2.1. 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 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. Evaluation and written performance appraisals of the IRB Director, Deputy Director and other IRB staff occur on an annual basis in accordance with institutional policies. In compliance with employment policy, institutional the evaluations are maintained within Human Resources under the jurisdiction of the Dean's Office, School of Medicine.

IRB Chairs will be evaluated biannually using a 360-degree assessment based on 5 criteria: 1) leadership, 2) participation, 3) technical knowledge, 4) teamwork, and 5) communication. This information will be maintained by the appropriate Institutional Official or designee.

All changes to IRB membership roster, including deletions, additions, and changes in role will be reported to OHRP in a timely manner by updating the Institutional Federal-wide Assurance and obtaining signature from the Institutional Official.

#### 2.2.1.1. Chairperson Responsibilities

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

#### 2.2.1.2. Vice-Chairperson

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

#### 2.2.1.3. IRB Members

- a. Review research applications and other appropriate materials prior to convened meetings.
- b. Provide sufficient advance notice if unable to attend a meeting.
- c. Attend convened meetings and contribute to Board discussion.
- d. Review studies according to approval criteria offered in the regulations and SOPP.
- e. Serve as primary, secondary reviewer or discussant on selected applications.
- f. Disclose any potential conflict of interest to the IRB chair as soon as it is recognized.
- g. Maintain confidentiality regarding any information contained in any review.
- h. Participate in project audits as needed.
- i. Review policies, procedures and forms on an annual basis.
- j. Understand these operating procedures and applicable federal, agency-specific (e.g., VA) and institutional regulations regarding human subjects research.

#### 2.2.1.4. HRPP Program Director/IRB Administrator

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

#### 2.2.1.5. HRPP Administrative Staff

- a. Maintain up-to-date knowledge of policies, procedures and regulations regarding human subjects research and IRB operations.
- b. Perform administrative duties to assure systematic flow of work through the IRB.
- c. Prepare and distribute review materials to members and consultants.
- d. Maintain files.
- e. Prepare and distribute minutes.
- f. Assure accurate and timely documentation, data input, and database up-keep.
- g. Send out notification of IRB decisions, requests for additional information, and correspondence to investigators in a timely manner.
- h. Send out timely reminders and notification to investigators when applications for study re-approval are due.

2.2.1.6. 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 cable modem service. IRB members will be allowed to use the notebook computer for the duration of their tenure and to obtain replacement computers when deemed necessary. All notebook computers remain property of the UC Regents. IRB members who leave the service of the committee are required to return the notebook computer to the HRPP.

2.2.2. Applicable Regulations

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

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

2.2.3. 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.

## 2.3. Orientation and Training

### 2.3.1. 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.

#### 2.3.1.1 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:

- a. UCSD HRPP Standard SOPP Manual
- b. UCSD IRB Factsheets on selected topics
- c. FDA Information Sheets and Guidelines when issued
- d. 45 CFR 46 (PHS/DHHS: Federal Policy for the Protection of Human Subjects)
- e. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects
- f. 21 CFR 50 (FDA: Protection of Human Subjects)
- g. 21 CFR 56 (FDA: Institutional Review Boards)
- h. 21 CFR 812 (FDA: Investigational Device Exemptions)
- i. 21 CFR 312 (Investigational New Drug Application)
- j. 38 CFR 16 (Protection Of Human Subjects, Common Rule)
- k. OPRR IRB Guidebook: Protecting Human Subjects
- l. OPRR Reports and Guidelines
- m. VHA Handbook 1200.5
- n. Other materials as appropriate

All IRB members will complete the UCSD online training modules (at <http://irb.ucsd.edu>) prior to starting as active members, and this will 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 him 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.

#### 2.3.1.2. 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.

### 2.3.1.3 Ongoing Educational Programs

The Human Research Protections Program Office has an ongoing educational program for both IRB members and investigators. Particular emphasis of training is placed on vulnerable populations including those with cognitive disabilities, children and prisoners. 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.

### 2.3.2. Applicable Regulations

2.3.3. Procedures

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

2.3.4. References, Forms, and Links

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

### **3. IRB Review Procedures**

#### **3.1. Initial Screening**

##### **3.1.1 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.

Individuals with any question about whether an activity represents “human subjects research” are to provide the IRB with a written description of the activity and request a determination. IRB staff will use the checklist “Determining Whether a Proposed Activity is Human Research According to DHHS or FDA Regulatory Definitions”

Applications that meet DHHS or FDA (or in the case of VA research, MCM 151-01) definitions of “human subjects” and “research” must be approved by an IRB.

Applications that meet the definition of “research involving human subjects” according to DHHS and FDA (or in the case of VA research, MCM 151-01) will be assigned 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 or Deputy Director. Should there not be at least one person present who is knowledgeable about or experienced in working with a specific field or population, or available as a consultant for a specific IRB meeting, the protocol will be deferred to another IRB committee or to another meeting of that committee where such expertise is present. 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, at minimum 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).

##### **3.1.2 Applicable Regulations**

[45 CFR 46.108](#)

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

##### **3.1.3 Procedures**

HRPP Protocol analysts will screen the application to determine if it qualifies as human subjects research or a clinical investigation based on the DHHS and FDA (or in the case

of VA research, MCM 151-01) definition of “research involving human subjects” and if necessary will use the worksheet “Determining Whether a Proposed Activity is Human Research According to the VA or FDA Regulatory Definitions.”

If the activity is not “human subjects research” as defined by DHHS, FDA, or in the case of VA research, MCM 151-01, it does not require review by the IRB. Investigators will be notified in writing if their application does not meet criteria for human research and therefore would not require IRB review.

Prior to full committee review, initial and continuing review applications will be screened by HRPP staff using a checklist to ensure that all applicability criteria (45 CFR 46.111) are satisfied and that the research represents one or more approvable categories of research under the expedited process. For application not meeting all applicability criteria, HRPP staff will notify the PI of any deficiencies in an attempt to rectify the deficiency prior to submitting the application for consideration by a convened IRB.

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

### 3.2. Full IRB review

#### 3.2.1 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 and exit the room while the project is being discussed.

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. The following documents should be made available to the primary reviewer: application facesheets, full research plan, informed consent documents, master plan and investigator brochure (if applicable), recruitment materials, and support letters (if applicable).

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. In addition, the IRB may limit accrual and require reporting back to the IRB prior to continuing research activities. The determination would be documented in approval correspondence and minutes.

When the convened IRBs requested substantive clarifications or modifications that were directly relevant to the determinations required by the IRB, the protocols cannot be approved without a review of the responsive information by a convened committee.

IRB members and consultants must self-disclose potential conflict of interest prior to reviewing protocols for which there may be conflict of interest. Each IRB member and consultant must sign a disclosure form on an annual basis and submit this form to the IRB Chair. This form includes any ownership interest (equity or stock options) of any amount in a company that could sponsor any research at this Institution when the value of the interest would be affected by the outcome of the research; compensation of any amount when the value of the interest would be affected by the outcome of the research; or board or executive relationship related to the research, regardless of compensation. Any member with a conflict of interest must disclose that conflict of interest before the project is discussed, and must abstain from voting and exit the room while the project is being discussed. IRB members and consultants cannot participate in the review of protocols in which they have a conflict of interest, except to provide information requested by an IRB.

#### 3.2.1.1. 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. The following documents should be made available to the primary reviewer: application facesheets, full research plan, informed consent documents, master plan, grant submission materials, and/or investigator brochure (if applicable), recruitment materials, and support letters (if applicable).

3.2.1.1.1 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. At least one IRB member will receive and review the DHHS-approved protocol (and sample consent if it exists). 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.

3.2.1.1.2 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.

3.2.1.1.3 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.

3.2.1.1.4 When the approval of research is contingent on specific minor conditions by the chairs or designee, this fact will be documented in the minutes of the first IRB meeting that took place after the date of the approval.

3.2.1.1.5 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.

3.2.1.1.6 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.

3.2.1.1.7 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.

3.2.1.1.8 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.

3.2.1.1.8.1. If research is being conducted at the VA, according to VA Policy, Payment for Subjects, the following conditions also apply:

VA policy prohibits paying human subjects to participate in research when the research is integrated with a patient's medical care and when it makes no special demands on the patient beyond those of usual medical care. Payment may be permitted, with IRB approval, in the following circumstances:

- (1) No Direct Subject Benefit. When the study to be performed is not directly intended to enhance the diagnosis or treatment of the medical condition for which the volunteer subject is being treated, and when the standard of practice in affiliated non-VA institutions is to pay subjects in this situation.
- (2) Others Being Paid. In multi-institutional studies, when human subjects at a collaborating non-VA institution are to be paid for the same participation in the same study at the same rate proposed.
- (3) Comparable Situations. In other comparable situations in which, in the opinion of the IRB, payment of subjects is appropriate.
- (4) Transportation Expenses. When transportation expenses are incurred by the subject that would not be incurred in the normal course of receiving treatment and which are not reimbursed by any other mechanism. b. Prospective investigators who wish to pay research subjects must in their proposal: (1) Substantiate that proposed payments are reasonable and commensurate with the expected

contributions of the subject; (2) State the terms of the subject participation agreement and the amount of payment in the informed consent form; and (3) Substantiate that subject payments are fair and appropriate, and that they do not constitute (or appear to constitute) undue pressure or influence on the perspective research subjects to volunteer for, or to continue to participate in, the research study; and that the payments do not constitute (or appear to constitute) coercion to participate in, or continue to participate in, the research study. c. The IRB and R&D Committee must review all proposals for payment of subjects to ensure conformity with VA policies. d. The VA Research Office is responsible for ensuring that IRB-approved payment to subjects is made from a VA approved funding source for research activities.

Payment to research participants for participation in studies is not considered a benefit, but a recruitment incentive. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive or present undue influence. Any credit for payment should accrue as the study progresses and not be contingent upon the participant completing the entire study. Unless it creates undue inconvenience or a coercive practice, payment to participants who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

Compensation for participation in a trial offered by a sponsor may not include a coupon good for a discount on the purchase price of the product once it has been approved for marketing. Payment to research participants for participation in studies is not considered a benefit, but a recruitment incentive. The amount and schedule of all payments should be presented to the IRB at the time of initial review. The IRB should review both the amount of payment and the proposed method and timing of disbursement to assure that neither are coercive nor present undue influence. Any credit for payment should accrue as the study progresses and not be contingent upon the participant completing

the entire study. Unless it creates undue inconvenience or a coercive practice, payment to participants who withdraw from the study may be made at the time they would have completed the study (or completed a phase of the study) had they not withdrawn.

While the entire payment should not be contingent upon completion of the entire study, payment of a small proportion as an incentive for completion of the study is acceptable, providing that such incentive is not coercive. The IRB should determine that the amount paid as a bonus for completion is reasonable and not so large as to unduly induce participants to stay in the study when they would otherwise have withdrawn.

All information concerning payment, including the amount and schedule of payment(s), should be set forth in the informed consent document.

3.2.1.1.9 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. In addition, payments designed to accelerate recruitment that are tied to the rate or timing of enrollment ("bonus payments.") are disallowed. Other types of compensation (e.g.: books, other non-cash gifts) must be disclosed and be approved by the IRB prior to implementation.

3.2.1.1.10 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:

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

3.2.1.1.11 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.

3.2.1.1.12 Review of Risk Level: Each proposal should be evaluated as to the level of risk imposed on study participants as either minimal risk or more than minimal risk. The IRB shall identify and analyze potential sources of risk and measures to minimize risk, including physical, psychological, social, legal, or economic risks. Analysis of risk includes measures that ensure that the risks to participants are reasonable in relation to potential benefits to participants and society, and are minimized by using procedures that are consistent with sound research design and that do not unnecessarily expose participants to risk.

### 3.2.1.2. 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 Pharmacopoeia (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:

- a. 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;
- b. 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;
- c. 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;
- d. 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

- e. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.
- f. 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).
- g. 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. When an IND is provided the reviewer will check this number to confirm that it is valid. This may be done by reviewing information provided by the investigator and/or sponsor such as the protocol or letter from the FDA or checked on the FDA website.

### 3.2.1.3. 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.

- 3.2.1.3.1. 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.
- 3.2.1.3.2. 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:
  1. could be life threatening,
  2. could cause permanent impairment of a body function,
  3. could cause permanent damage to body structure, or
  4. could necessitate medical or surgical intervention to preclude permanent impairment of a body function or preclude permanent damage to body structure.
- h. When an IDE is provided the reviewer will check this number to confirm that it is valid. This may be done by reviewing information provided by the investigator and/or sponsor such as the protocol or letter from the FDA or checked on the FDA website.

3.2.1.3.3. Exempted Devices: 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. 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.
- b. 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.
- c. 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.

- d. 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.
- e. A device intended solely for veterinary use.
- f. A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c).
- g. 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.

### 3.2.2. Approval and Documentation

The IRB will vote according to the categories of action described in these SOPP. Categories of Action are defined in Section 4.2 of this document. 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. Documentation should include the basis for requiring revision to the application or reason for disapproval of the research.

### 3.2.3. Distribution of Relevant Materials to IRB Members

All IRB members will be provided with all available information relevant to initial review. Relevant materials are to be provided for all types of IRB review including initial review, amendments, reports, responses, and continuing review. This includes, but is not limited to:

- 1) The research plan
- 2) Consent documents or request for waiver of consent, as permitted by 45 CFR 46.116(d)

- 3) Related grant applications or progress reports available at the time of the IRB application,
- 4) Subject surveys or questionnaires,
- 5) Supporting documentation from sponsors,
- 6) Advertisements or other information provided to study participants,
- 7) Drug-related information such as Investigator's Brochures or package inserts,
- 8) Any other information known to be relevant to the scientific merit, determination of safety, risk, and benefit of the study,
- 9) Access to electronic review forms, checklists, and supplemental regulatory documents,
- 10) Subject recruitment materials, flyers, advertisements.

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.

#### 3.2.4. Applicable Regulations

<a href="#">21 CFR 812.2(b)(1)(ii)</a>	<a href="#">45 CFR 46.111</a>
<a href="#">21 CFR 812.66</a>	<a href="#">38 CFR 16.108 (a)</a>
<a href="#">21 CFR 814.124(a)</a>	<a href="#">38 CFR 16.103 (b) (4-5)</a>
<a href="#">21 CFR 56.107(e-f)</a>	<a href="#">38 CFR 46.107 (a, e, f)</a>
<a href="#">21 CFR 56.108(a)(1-2)</a>	<a href="#">38 CFR 16.108 (b)</a>
<a href="#">21 CFR 56.108(c)</a>	<a href="#">38 CFR 16.109 (a-e)</a>
<a href="#">21 CFR 56.109(a-f)</a>	<a href="#">38 CFR 16.111</a>
<a href="#">45 CFR 46.108 (a)</a>	<a href="#">ICH 3.1</a>
<a href="#">45 CFR 46.103 (b) (4-5)</a>	<a href="#">California Health and Safety Code</a>
<a href="#">45 CFR 46.107 (e, f)</a>	<a href="#">445</a>
<a href="#">45 CFR 46.108 (b)</a>	
<a href="#">45 CFR 46.109 (a-e)</a>	

#### 3.2.5. Links

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

### 3.3. **Criteria for Approval of Research Projects**

#### 3.3.1 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. Research cannot

commence until fully approved by the IRB (and VA R&D Committee for VA projects). Approval occurs when the HRPP releases an approval letter containing the approval date.

#### 3.3.1.1. 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 from various populations and sub-populations, as applicable. 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. They will consider whether inclusion and exclusion criteria impose fair and equitable burdens and benefits. 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. The committee may disallow non-veterans to be entered into VA-approved research studies except when there are insufficient veterans available to complete the study. VA policy does not currently permit research involving pregnant women or fetuses.
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.

8. For studies supported by a commercial entity, the legal, contractual, and institutional risks have been found to be limited based upon review of the agreement between the institution and study sponsor.

#### 3.3.1.2. Additional Criteria:

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

1. The IRB will consider participant's privacy interests in reviewing the recruitment, consenting, and medical procedures described in the research plan. Research plans must include a description of how participant privacy will be protected. Investigators must disclose their process for ensuring that participants have control over access to themselves when applicable. Some examples of the types of questions the Committee should ask about the research when determining the adequacy of managing participant's privacy concerns include:
  - a. Where the participants will be recruited? Will recruitment take place in an open public area, a crowded waiting room, or other venue that would jeopardize participant privacy?
  - b. Where will the participant be consented? Will the informed consent process take place in a private room, where participant can ask questions without feelings of embarrassment or discomfort?
  - c. If the research involves a physical exam, will the patient be provided with a room or private space to undress and dress? Who will be in the exam room?
  - d. For research involving young children, will the parent be allowed to be present if this makes the child more comfortable? For adolescents, will the participant be able to talk privately to the researcher without parental supervision or intrusion?
2. 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.
3. 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.
4. 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.

5. 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.
6. The IRB will also consider the following criteria during initial review, as appropriate to the type of study being proposed. These criteria are assessed for each protocol using a checklist associated with each project and available to the IRB reviewer electronically:
  - a. Whether the purpose of study is clear.
  - b. Results of any related studies
  - c. The number of subjects and duration of participation is stated and appropriate.
  - d. Duration of the study and frequency of activities are clear and appropriate.
  - e. Wash-out period for medications is appropriate and safeguards are in place to assure subject's condition will be adequately monitored during that period.
  - f. Use of placebo is appropriate.
  - g. The setting in which research occurs is appropriate.
  - h. Plan for recruiting subjects including recruitment and enrollment procedures and appropriateness of claims made in advertising.
  - i. The nature or amount of the compensation offered to subjects for participation in research does not create undue influence, particularly for economically disadvantaged subjects.
  - j. The risks of research activities are clearly distinguished from the risk of relevant standard healthcare.
  - k. Physical, psychological, social and economic risks, including risks to privacy and the probability of occurrence posed by research design, interventions and procedures.
  - l. 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.
  - m. Attestation, when required, by the investigator as to whether the proposal, or one substantially similar to it, has been disapproved by another IRB.
  - n. Process for monitoring and reporting adverse events.
  - o. Presence of a Data Safety Monitoring Board (DSMB) if applicable.
  - p. Information to be used for recruitment or to inform subjects or potential subjects about the nature of the research.
  - q. The investigator and research staff has appropriate scientific and human subject protection training to conduct the study.
  - r. Investigator potential financial conflicts.
7. For VA-funded studies, non-veteran subjects may be included if approved by VA R&D Committee and there is documented justification for including non-veteran subjects. The committee may disallow non-veterans to be entered into VA-approved research studies except when there are insufficient veterans available to

- complete the study. VA R&D Committee must consider VA responsibilities in the event of research-related injury to non-veteran participants.
8. For VA studies, a witness to the participant's signature or the participant's legally authorized representative's signature must sign and date the consent document.
  9. If the sponsor or IRBs required a witness to the consenting process in addition to the witness to the participant's signature and if the same person needed to serve both capacities, a note to that effect must be placed under the witness's signature line.
  10. A statement that a copy of the signed and dated consent document would be given to the person signing the consent document.

In general, IRB approval cannot occur unless the IRB is able to determine based on information presented that the investigator obtained the legally effective informed consent of the participant or the participant's legally authorized representative; the circumstances of the consent process provided the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate; the circumstances of the consent process minimized the possibility of coercion or undue influence; the individuals communicating information to the participant or the legally authorized representative during the consent process provided that information in language understandable to the participant or the representative; the information being communicated to the participant or the representative during the consent process did not include exculpatory language through which the participant or the legally authorized representative was made to waive or appear to waive any of the participant's legal rights. The informed consent process will be periodically reviewed for select studies by the IRB or designated reviewers, such as VA or UCSD auditors. Report findings will be shared with the IRB Steering Committee or as delegated, and with VA R&D Committees, as appropriate.

### 3.3.2. Applicable regulations

[21 CFR 812.2\(b\)\(1\)\(ii\)](#)

[21 CFR 812.66](#)

[21 CFR 56.108\(a\)\(1-2\)](#)

[45 CFR 46.109 \(a-e\)](#)

[45 CFR 46.111](#)

[38 CFR 16.103 \(b\) \(4-5\)](#)

[38 CFR 16.111](#)

[ICH 3.1](#)

### 3.3.3. 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

## 3.4. **Informed Consent**

### 3.4.1. 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. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent to another individual knowledgeable about the research. The investigator remains ultimately responsible, even when delegating the task of obtaining informed consent to another individual knowledgeable about the research.

In order to assess the informed consent process, the submission should be detailed enough to allow for IRB determination. In addition to providing a description of the consent process including the person who would conduct the consent interview, and the information to be communicated to the prospective participant or the legally authorized representative, the research plan should include the person who would provide consent or permission; any waiting period between informing the prospective participant and obtaining consent; steps taken to minimize the possibility of coercion or undue influence; the language used by those obtaining consent; and, the language understood by the prospective participant or the legally authorized representative.

The informed consent process may be periodically audited by the IRB or appropriate compliance or designated personnel to assess conduct. Information presented in order for the IRB to approve research will be reviewed and must include, but is not limited to the following. a) The investigator obtained the legally effective informed consent of the participant or the participant's legally authorized representative. b) The circumstances of the consent process provided the prospective participant or the legally authorized representative sufficient opportunity to consider whether to participate. c) The circumstances of the consent process minimized the possibility of coercion or undue influence. d) The individuals communicating information to the participant or the legally authorized representative during the consent process provided that information in language understandable to the participant or the representative. e) The information being communicated to the participant or the representative during the consent process did not include exculpatory language through which the participant or the legally authorized representative was made to waive or appear to waive any of the participant's legal rights.

All amendments to the project or changes in the informed consent must be reviewed and approved by the IRB prior to initiating the changes, except when necessary to eliminate immediate hazard(s) to the subject(s). If the amendment addresses an issue related to biosafety or radiation safety, the appropriate committee or subcommittee must first approve the amendment. The IRB must document in the minutes sufficient justification of any deletion or substantive modification of information concerning risks or alternate procedures contained in the approved informed consent document.

#### 3.4.1.1. 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 signed

informed consent form and bill of rights will be given to the person signing the form, and the original placed in the archival research record maintained by the PI.

For VASDHS clinical research a copy of the consent form must be placed in the patient's VA medical record. The IRBs may make a determination to not require the participant's medical record (electronic or paper) to be flagged if (1) The subject's participation in the study involves: (a) Only one encounter, (b) Only the use of a questionnaire, or (c) The use of previously collected biological specimens. (2) The identification of the patient as a subject in a particular study (if the study greater than minimal risk) would place the subject at greater than minimal risk.

The consent form may be either of the following:

- a. 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 and ask questions before it is signed.
- b. 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. The short form must be signed by the subject (or the representative) and dated in order for it to be approved. 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 intervention 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 or representative appeared capable of understanding, and a statement that the subject was given the opportunity to ask questions, and documentation that consent was obtained before any subject procedures were performed. Unless specifically waived by the IRB, VA research studies must document the informed consent process by a "Research / Informed Consent" progress note that includes the information listed above.

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.

#### 3.4.1.2. 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 8<sup>th</sup> grade reading level or lower.

### 3.4.1.3. 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 is 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.
11. 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.

#### 3.4.1.4. 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:

1. The research involves no more than minimal risk
2. Granting of waiver will not adversely affect privacy rights and welfare of the individuals whose records will be used.
3. The project could not practicably be conducted without a waiver
4. The project could not practicably be conducted without use of PHI
5. The privacy risks are reasonable relative to the anticipated benefits of research
6. An adequate plan to protect identifiers from improper use and disclosure is included in the research proposal
7. An adequate plan to destroy the identifiers at the earliest opportunity, or justification for retaining identifiers, is included in the research proposal
8. The project plan includes written assurances that PHI will not be re-used or disclosed for other purposes.
9. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

Many DHHS multi-site studies such as cooperative oncology trials, cardiology trials, and behavioral studies, include a consent document that has been approved by DHHS. The approved consent document must include all information concerning risks or alternative

procedures contained in the DHHS-approved sample consent document, unless the IRB has justified in the minutes any deletion or substantive modification of that information.

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:

1. 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. Each subject must be asked whether the subject wants documentation linking the subject with the research, and the subject's wishes will govern, or
2. 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 review the written statement and 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.

#### 3.4.1.5. 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.

3.4.1. 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](#)

3.4.2. 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>

**3.5. Emergency Use and Informed Consent and Emergency Exemption from Prospective IRB Approval**

3.5.1. Policy

3.5.1.1. Emergency Use

The criteria allowing unplanned emergency use of a test article in a life threatening situation are listed in the checklist “Criteria Allowing Unplanned Emergency Use of a Test Article in a Life Threatening Situation.” Investigators who want to use a test

article in an emergency basis in a life threatening situation are to follow this checklist. Whenever possible, investigators are to contact the IRB chair in advance of the use.

For prior notifications the IRB chair uses the “Criteria Allowing Unplanned Emergency Use of a Test Article in a Life Threatening Situation” to determine whether the circumstances of the use meet regulatory criteria.

1. If the IRB chair determines that circumstances of the use meet regulatory criteria, the IRB chair informs the investigator and clears them to proceed without IRB review.
2. If the IRB chair determines that circumstances of the use do not meet regulatory criteria, the IRB chair informs the investigator and indicates that proceeding with the use without IRB approval will be serious non-compliance.

Investigators are to submit 5-day reports of emergency uses to the IRB. The IRB chair uses the “Criteria Allowing Unplanned Emergency Use of a Test Article in a Life Threatening Situation” to determine whether the circumstances of the use described in the 5-day report meet regulatory criteria.

1. If the IRB chair determines that circumstances of the use meet regulatory criteria, the IRB chair informs the investigator in writing.
2. If the IRB chair determines that circumstances of the use do not meet regulatory criteria, the IRB chair informs the investigator in writing that the use without IRB approval is serious non-compliance, and refers the matter to the convened IRB for review under the policy and procedure on “Non-compliance.”

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. The VA does not allow planned emergency research (which requires waiver of consent) to be conducted in VA facilities. VASDHS investigators will comply with relevant VA policy on research in emergency settings.

#### 3.5.1.2. 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:

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

3. Time was not sufficient to obtain consent from the subject's legal representative.
4. 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.

#### 3.5.1.2.1. Exception 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:

1. 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.
2. Obtaining informed consent is not feasible because:
  - a. The subjects will not be able to give their informed consent as a result of their medical condition;
  - b. The intervention under investigation must be administered before consent from the subjects' legally authorized representatives is feasible; and
  - c. There is no reasonable way to identify prospectively the individuals likely to become eligible for participation in the human subjects research.
3. Participation in the research holds out the prospect of direct benefit to the subjects because:
  - a. Subjects are facing a life-threatening situation that necessitates intervention;

- b. 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
  - c. 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.
- 4. The human subjects research could not practicably be carried out without the waiver.
- 5. The proposed investigational plan:
  - a. Defines the length of the potential therapeutic window based on scientific evidence, and,
  - b. The investigator has committed to attempting to contact a legally authorized representative for each subject within that window of time and;
  - c. If feasible, the investigator has committed to asking the legally authorized representative contacted for consent within that window rather than proceeding without consent;
  - d. 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.
- 6. 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.
- 7. Additional protections of the rights and welfare of the subjects will be provided, including, at least:
  - a. 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;
  - b. 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;
  - c. 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;
  - d. Establishment of an independent data monitoring committee to exercise oversight of the human subjects research; and
  - e. 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 .

### 3.5.2. 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](#)

### 3.5.3. Procedures

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

### **3.6. Privacy and Confidentiality of Research Records**

#### **3.6.1. 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. Regarding access to personal information, the IRB will consider the methods for reducing potential privacy concerns when the private information prior to approval, when the personal information: 1) is being accessed without the participant’s knowledge and explicit permission, e.g., under a waiver of consent or

HIPAA authorization, before consent, during recruitment and screening, under an exempt protocol; 2) concerns sensitive information; 3) involves covert observation of non-public activity.

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.

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.

IRB staff and IRB members use the Submission Checklist and Reviewer Checklist to assist them during the review. When the only or primary risk to a participant relates to his or her privacy, the IRB review places added emphasis in eliciting what private information is involved in the protocol and how it will be used. Adequate provisions to protect the privacy interests of potential participants and participants are required from the screening and recruitment phases throughout data analysis and retention. If the protocol does not include adequate provisions to protect the privacy interests of the participants, the IRBs may not approve the protocol as written.

### 3.6.2. Waiver of Authorization to Use PHI for Research: HIPAA waiver

UC system-wide policy on Disclosure of PHI for Research Purposes adopted by UCSD permits the disclosure of PHI to a researcher without patient authorization under the following circumstances:

1. The IRB approved and certified a Waiver of Authorization; or
2. The IRB approved the protocol using a limited data set and with a data use agreement between the researcher and UCSD; or
3. The IRB approved the protocol using de-identified data; or
4. The research involves PHI of decedents; or
5. For the purpose allowed under law, such as notification of adverse events

To use or disclose PHI with an IRB approved Waiver of Authorization of the individual's Authorization, UCSD must receive from the researcher requesting the disclosure of PHI, and IRB letter of Approval that certifies all of the following:

1. Identification of the IRB and the date on which the Waiver of Authorization was approved;
2. A brief description of the PHI for which use or access has been determined to be necessary;
3. A statement that the Waiver of Authorization has been reviewed and approved by the IRB;
4. The signature of the chair or other member as designated by the IRB chair who certifies the Waiver of Authorization; and
5. A statement that the IRB has determined that the Waiver of Authorization satisfies the three waiver criteria in the privacy rule.
  - a. Use or disclosure of PHI involves no more than a minimal risk to the privacy of individuals based on the presence of the following elements:
    - i. An adequate plan to protect the identifiers from improper use and disclosure;
    - ii. An adequate plan to destroy the identifiers at the earliest opportunity consistent with conduct of the research;
    - iii. Adequate written assurances that the PHI will not be reused or disclosed to any other person or entity;
  - b. The research could not practicably be conducted without the waiver; and
  - c. The research could not practicably be conducted without access to and use of PHI.

According to UC policy (Policy Implementation 9-11), UCSD healthcare providers may discuss with a patient the possibility of enrolling in a research protocol if the researcher is a covered health care provider who seeks an IRB Waiver of Authorization to obtain the individual's contact information. The IRB can waive authorization for this purpose, even if the research protocol requires the individual's Authorization to participate

### 3.6.3. 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:

1. Information relating to sexual attitudes, preferences, or practices;
2. Information relating to the use of alcohol, drugs, or other addictive products.
3. Information pertaining to illegal conduct;
4. Information that if released could reasonably be damaging to an individual's financial standing, employability, or reputation within the community;
5. 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;
6. Information pertaining to an individual's psychological well-being or mental health.

#### 3.6.4. Data De-identification

HIPAA contains in Section 164.514 a “safe harbor” provision that states information may be considered “de-identified” i.e., 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

### 3.6.5. Applicable Regulations

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

<http://aspe.hhs.gov/admsimp/bannerps.htm>

<http://www.hhs.gov/ocr/hipaa/research.html>

The Federal Register/Volume 65; Number 250/ Thursday, December 28, 2000/Rules and Regulations/ page 82816-82817 located at:

<http://www.hhs.gov/ocr/part8.pdf>

### 3.6.6. 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, MSC 9653 Bethesda, Maryland 20892-9653 Telephone: (301) 443-2578 Website for Certification Information: <a href="http://www.nimh.nih.gov/research/confident.cfm">http://www.nimh.nih.gov/research/confident.cfm</a>

### **3.7. Review of Projects Involving Protected Populations**

#### **3.7.1. 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 (e.g.: 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:

1. any monetary payments to subjects are not so great as to constitute an undue inducement;
2. the proposed safeguards are adequate to protect the rights and welfare of the subjects;
3. minorities receive an equal share of the benefits of research and do not bear a disproportionate burden;
4. 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.

#### **3.7.2. 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. HRPP strongly encourages the Principal Investigator to contact HHS and speak to Julia Gorey, J.D. (240-453-8141) about applying for HHS approval for inclusion of prisoners or wards of the court in research.

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.

### 3.7.3. Students and Employees

#### 3.7.3.1. Policy

Students (undergraduate, graduate, and medical students), and employees of UCSD, VASDHS, 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.

#### 3.7.3.2. Applicable Regulations

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

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

### 3.7.3.3. Procedures

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

### 3.7.4. Review of Projects Involving Pregnant Women

#### 3.7.4.1. 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.

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 non-pregnant 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.

#### 3.7.4.2. 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](#)

#### 3.7.5. Review of Projects Involving Fetuses or Fetal Tissue

##### 3.7.5.1. 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:

1. *Human fetal tissue* means tissue or cells obtained from a dead embryo or fetus after a spontaneous or induced abortion, or after a stillbirth.
2. 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.
3. 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.

4. 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.
5. 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.
6. 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:

1. 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.)

2. 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.

3.7.5.2. Applicable Regulations

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

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

3.7.5.3. Procedures

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

3.7.6. Review of Projects Involving Children and Adolescents

3.7.6.1. Definitions

For purposes of this policy the following definitions are used, consistent with federal (45 CFR part 46 subpart D) 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. In California, a guardian may be a biological or adoptive parent or a legally appointed guardian. For wards of the court, usually an order from the judge is required in addition to permission from the person charged with care of the child.
5. "Minors" are people under 18 years of age. In California, minors generally may not consent to medical care or treatment, or research involving medical care or treatment, without a parent or legal guardian's permission. However, federal regulations interpreted with California legal exceptions, may permit minors in the following categories to consent to research:
  - a) "Emancipated Minor" is a person under age 18 who has been legally married, on active duty in the U.S, Armed forces, or emancipated by court order (California Family Code 7002).
  - b) "Self-Sufficient minor" is a person between age 15 and 18 living apart from parent or guardian, managing his or her own financial affairs, and not dependent on parents or guardian for medical care. (California Family Code 6922)
  - c) Minors, 12 years or older, seeking care for certain condition or diseases (see California Family Code 6924-6929)

#### 3.7.6.2. 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 will determine whether proposed research participants meet the federal and state definitions of "child", "emancipated" or "self-sufficient" minor, and are permitted by California law to consent to research. The Principal Investigator is responsible for determining whether specific individuals involved in research (minors and guardians) are qualified to provide permission or assent. 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. In addition, the IRB will document the conditions of parental and child or adolescent assent. In general, permission should be obtained from both parents before a child is enrolled in research. However, the Institutional Review Board (IRB) may find that the permission of one parent is sufficient for research to be conducted under 46.404 (minimal risk) or 46.405 (greater than minimal risk, direct benefit). When research is to be conducted under 46.406 and 46.407 permission must be obtained from both parents, unless one parent is deceased, unknown, incompetent, or not reasonably available, or when only one parent has legal responsibility for the care and custody of the child. The IRB will evaluate and document the conditions of parental and child or adolescent assent. This information will be reflected in correspondence to the investigators and in the IRB minutes.

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.

3.7.6.3. Applicable Regulations

[45 CFR 46. Subpart D](#)

[VHA Directive 2001-028](#)

3.7.6.4. Procedures

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

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

3.7.7.1. 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 and Section 24178 of the California Health and Safety Code that specifies the requirements for and procedures related to the surrogate consent process.

Surrogate decision makers may be used when all of the following are true according to Section 24178 of the California Health and Safety Code:

- 1) Informed consent has not been waived by the IRB
- 2) The individual is unable to consent and does not express dissent or resistance to participation
- 3) The individual is not an inpatient on a psychiatric unit or in a mental health facility or a patient on a psychiatric hold
- 4) The research involves medical experimentation (not treatment)
- 5) The medical experiments relate to the cognitive impairment, lack of capacity, or serious or life-threatening diseases and condition of research participants.

During IRB review of VA research involving persons with impaired decision-making capacity, the membership must include at least one member who is an expert in the area of the research (VHA 1200.5 app. D 6b(1)).

Additionally, VA requirements specifically address that research involving subjects who are mentally ill or subjects with impaired decision-making capacity warrants special attention. When reviewing research involving these the IRB membership must include at least one member who is an expert in the area of the research.

Consideration may be given to adding another member who is a member of the population, a family member of such a person or a representative of an advocacy group for that population. The IRB may utilize ad hoc members as necessary to ensure appropriate expertise. For VA studies, research involving persons with impaired decision-making capability may only be approved when the following conditions apply:

- (1) Only incompetent persons or persons with impaired decision-making capacity are suitable as research subjects. Competent persons are not suitable for the proposed research. The investigator must demonstrate to the IRB that there is a compelling reason to include incompetent individuals or persons with impaired decision-making capacity as subjects. Incompetent persons or persons with impaired decision-making capacity must not be subjects in research simply because they are readily available.
- (2) The proposed research entails no significant risks, tangible or intangible, or if the research presents some probability of harm, there must be at least a greater probability of direct benefit to the participant. Incompetent people or persons with impaired decision-making capacity are not to be subjects of research that

imposes a risk of injury, unless that research is intended to benefit that subject and the probability of benefit is greater than the probability of harm.

- (3) Procedures have been devised to ensure that participant's representatives are well informed regarding their roles and obligations to protect incompetent subjects or persons with impaired decision making capacity. Health care agents (appointed under Durable Power of Attorney for Health Care (DPAHC)) and next-of-kin, or guardians, must be given descriptions of both proposed research studies and the obligations of the person's representatives. They must be told that their obligation is to try to determine what the subject would do if competent, or if the subject's wishes cannot be determined, what they think is in the incompetent person's best interest.

The IRB must make a determination in writing of each of the criteria listed in above (Handbook 1200.5 subparagraph 6c). If these criteria are met, the IRB may approve the inclusion of incompetent subjects or subjects with impaired decision-making capacity in research projects on the basis of informed consent from authorized representatives as defined in paragraph 11 of the VHA Handbook.

Both investigators and IRB members must be aware that for some subjects, their decision-making capacity may fluctuate. For subjects with fluctuating decision making capacity or those with decreasing capacity to give consent, a re-consenting process with surrogate consent may be necessary.

Although incompetent to provide informed consent, some persons may resist participating in a research protocol approved by their representatives. Under no circumstances may subjects be forced or coerced to participate.

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](http://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. In the event that a protocol may enroll subjects with diminished capacity to consent, the protocol should identify a plan for seeking the subject's assent. The IRB should evaluate whether assent of the participants is a requirement, and if so, whether the plan for assent is adequate. Mere failure to object should not, absent affirmative agreement, be construed as assent. Under no circumstances may a subject be forced or coerced to participate in a research study.

#### 3.7.7.2. Determination of decisional capacity

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

1. evidence a choice;
2. understand relevant information;
3. appreciate the situation and its likely consequences; and
4. 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. An example of a formal procedure could be a 5 to 10-item questionnaire read by the person administering the consent to the prospective subject that includes questions about key elements of the research (e.g. Name two study procedures. What do you do if you no longer want to be in the study? What alternatives are there to participating). Prospective subjects having adequate decisional capacity to provide informed consent must answer these questions correctly. Less formal procedures could include the ways professionals often make judgments about capacity in routine interactions.

For VA research studies, the VA Handbook 1200.5 must be considered when accepting surrogate consent. For VA studies, surrogate consent may only be accepted when the 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:

1. The practitioner, in consultation with the service chief, may determine after appropriate medical evaluation that the prospective research subject lacks decision-making capacity and is unlikely to regain it within a reasonable period of time.
2. Consultation with a psychiatrist or licensed psychologist must be obtained when the determination that the prospective research subject lacks decision-making capacity is based on a diagnosis of mental illness.
3. All disclosures that are required to be made to a competent subject by the investigator must be made to the subject's surrogate.
4. If feasible, the practitioner must explain the proposed research to the prospective research subject even when the surrogate gives consent. Under no circumstances may a subject be forced or coerced to participate in a research study.

#### 3.7.7.3.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*

### 3.7.7.3.1. Identifying Persons to Provide Surrogate Consent

#### 3.7.7.3.1.1. 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. Note that, although VA follows state law in accepting the priority of potential surrogates, the only adult relative acceptable in category 9 is a grandparent (VHA Handbook 1200.5 § 11a(2)).

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:

1. Has reasonable knowledge of the subject;
2. Is familiar with the subject's degree of impairment;
3. Is willing to serve as the substitute decision-maker;
4. Understands the risks, potential benefits, procedures and available alternatives to research participation;
5. 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.

#### 3.7.7.3.1.2. 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.

### 3.7.7.3.2. 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.

#### 3.7.7.4. 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:

1. A subject who regains the cognitive ability to consent must be re-consented using standard consenting procedures.
2. 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.
3. 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.

#### 3.7.7.5. Applicable Regulations

[VHA Handbook 1200.5](#)  
[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.](#)

[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.](#)

### 3.7.7.6. 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.

## 3.8. **Financial Disclosure and Conflict of Interest**

### 3.8.1. Policy

#### 3.8.1.1. 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 sub-investigator), 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. This policy applies to all IRB members and consultants retained for the purpose of providing scientific review of proposed research.

### 3.8.1.2. 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.

For the purpose of this document, *Significant Financial Interest* means anything of monetary value, including but not limited to, salary or other payments for services (e.g., consulting fees or honoraria); equity interests (e.g., stocks, stock options or other ownership interests); and intellectual property rights (e.g., patents, copyrights and royalties from such rights). The term does not include: Salary, royalties, or other remuneration from the applicant institution; Any ownership interests in the institution, if the institution is an applicant under the SBIR Program; Income from seminars, lectures, or teaching engagements sponsored by public or nonprofit entities; Income from service on advisory committees or review panels for public or nonprofit entities; An equity interest that when aggregated for the Investigator and the Investigator's spouse and dependent children does not exceed \$10,000 in value as determined through reference to public prices or other reasonable measures of fair market value, and does not represent more than a five percent ownership interest in any single entity; and salary, royalties or other payments that when aggregated for the Investigator and the Investigator's spouse and dependent children over a twelve month period are not expected to exceed \$10,000.

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.

### 3.8.1.3. Review and Management of Conflicts of Interest

The IRB must ensure that steps to manage, reduce, or eliminate potential or real conflicts of interest have been taken. These steps are taken during the review process. 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 and the PHS awarding agency for PHS-funded research. 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.

### 3.8.2. Applicable Regulations

[42 CFR 50.601-607](#)

[21 CFR 54.4-6](#)

### 3.8.3. Procedures

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

## 3.9. **Exemption from IRB Review**

### 3.9.1. 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:
  - a. information obtained is recorded in such a manner that human subjects can be identified, directly or through identifiers linked to the subjects; and
  - b. 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:
  - a. the human subjects are elected or appointed public officials or candidates for public office; or
  - b. 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:
  - a. public benefit or service programs;
  - b. procedures for obtaining benefits or services under those programs;
  - c. possible changes in or alternatives to those programs or procedures; or
  - d. 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,
  - a. if wholesome foods without additives are consumed or
  - b. 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.

### 3.9.2. Applicable Regulations

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

### 3.9.3. 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.

## **3.10. Expedited Review**

### 3.10.1. 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; however the reviewer of an expedited project may not disapprove the research. Only a fully convened committee can disapprove a research project. A determination may be made that full committee review is required although the criteria below is met.

#### 3.10.1.1. Categories of Research Appropriate for Expedited Review

##### 3.10.1.1.1. 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. Research on drugs for which an investigational new drug application (21 CFR 312) is not required.
  - a. 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, electromyogram, 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 non-research 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.

#### 3.10.1.1.2. 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.

#### 3.10.1.1.3. 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:

1. 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
2. no subjects have been enrolled and no additional risks have been identified; or
3. the remaining research activities are limited to data analysis; or
4. 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
5. the research initially qualified for expedited review and there have been no changes that would increase the risk.

#### 3.10.1.1.4. 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.

#### 3.10.1.1.5. Modifications in Advertisements

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

#### 3.10.1.1.6. 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.

#### 3.10.1.1.7. 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:

1. 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
2. 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.
3. 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.

### 3.10.1.2. 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. The Chair or designee must review the full set of documents submitted by the investigator in reaching a decision during an expedited review.

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.

The Principal Investigator must submit the following documents to the HRPP for consideration of expedited review: application facesheets, full research plan, informed consent documents, master plan and investigator brochure (if applicable), recruitment materials, and support letters (if applicable) related grant applications or progress reports available at the time of the IRB application, subject surveys or questionnaires, supporting documentation from sponsors, drug-related information such as package inserts, any other information known to be relevant to the scientific merit, determination of safety, risk, and benefit of the study.

Reviewers evaluating research under the expedited process either as an initial or continuing review must determine that all applicability criteria (45 CFR 46.111) are satisfied and that the research represents one or more approvable categories of research under the expedited process. Reviewers cannot disapprove research under the expedited review process.

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 SOPP continue to apply to research reviewed under the expedited review process.

Considerations for identifying and managing conflict of interest for expedited reviews follow the same procedures as with full reviews. When the Chair or designee discloses any conflict of interest, the Chair or designee cannot participate in the review.

### 3.10.2. 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

### 3.10.3. Procedures

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

## 3.11. **Continuing Review**

### 3.11.1. 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 48 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 an **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.

#### 3.11.1.1. Interim Report

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.

#### 3.11.1.2. 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. For VA studies, the VA ACOS/RD will be informed of the IRB determination.

As stated above, when an investigator does not provide continuing review information to the IRBs or the IRB has not approved continuation, IRBs must ensure that all activities including recruitment, advertisement, screening, consent, and collection of private identifiable data are stopped. The IRBs must notify investigators to submit immediately to the IRB chair, a list of participants for whom stopping research activities would cause harm, if applicable. Upon IRB Chair approval (and for VA studies, in consultation with the Chief of Staff), the IRB may allow current participants to continue interventions or interactions if the IRB finds an over-riding safety concern or ethical issue involved such that it is in the best interests of individual participants to continue participating.

#### 3.11.1.3. 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.

#### 3.11.1.4. 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:

1. other unexpected events related to the safety of subjects,
2. all significant deviations from the protocol, good clinical practice, applicable regulations or institutional policies involving the conduct of the study or subject participation,
3. summaries of the DSMB findings, if a DSMB is used,
4. 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. Reporting to ORO is via the VASDHS Director through the ACOS/R&D.

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.

#### 3.11.1.5. 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. At least one IRB member leads the discussion regarding the review, and is provided with and reviews the complete protocol. The assigned primary reviewer leads the discussion of the protocol during the meeting. All IRB members will receive the information necessary to enable them to conduct a review in enough depth to be able to discuss the protocol at the meeting.

The PI must submit the following materials to the HRPP office Routine for continuing review:

1. 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.

Specifically, the IRB must determine that any significant new findings that arose from the review process and that might relate to participants' willingness to continue participation was provided to participants, if applicable.

2. 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.
3. A copy of the study protocol currently in use.
4. Approved or proposed amendments, including minor changes, (if any) and the IRB action on each amendment.
5. Number of subjects enrolled in the study.
6. Research findings to date.
7. Adverse event reports from investigators, sponsor safety reports (e.g., IND or IDE Safety Reports).
8. Documentation of protocol violations and/or deviations, or non-compliance with applicable regulations in the study file.
9. All reports of injuries to subjects, unanticipated problems, complaints from subjects or others, new scientific findings, or any information that may change the risk/benefit ratio for subjects.
10. A statement from the investigator that all SAEs and unexpected adverse drug experiences have been reported as required.
11. Amended or updated Investigator Brochures.
12. 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.
13. Any new recruitment documents.
14. 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.

All necessary information relevant to the assessment of the project’s risks and benefits to study participants will be reviewed by the primary reviewer and an analyst assigned to the IRB committee.

Based on its review of the above information the IRB determines for each approved research protocol whether the research is re-approved, requires modifications to secure reapproval, is suspended or disapproved (terminated) based on assessment of the project’s risks and benefits. 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.

### 3.11.2. 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](#)

### 3.11.3. Procedures

Person(s) Responsible	Procedures
IRB Chair IRB Members	<p><b>Project Reviews</b></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>
IRB Administrator or staff designee	<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>

### 3.12. Protocol Amendments

#### 3.12.1. Policy

Investigators must submit a complete description of proposed modifications to a project for review. At least one IRB member leads the discussion regarding the review, and is provided with and reviews the complete protocol. Due to the nature of the e-IRB process, which involves conversion of documents to PDF format for electronic review, all documentation is also made to all other IRB members when the agendas are posted.

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.

For protocols involving investigational drugs or devices, an amendment or protocol change intended to eliminate an apparent immediate risk or danger to participants may be implemented immediately provided the FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 21 CFR 56.104(c). The amendment must undergo full IRB review at the earliest opportunity.

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.

### 3.12.2. Process for Conducting Continuing Review

When reviewing project amendments, the IRB will assess all of the same criteria for approval that were evaluated during initial review. At least one IRB member is provided with and reviews the complete protocol. The e-IRB process involves conversion of documents to PDFs for electronic review so that all documentation is also made available to all members of the IRB when the meeting agendas are posted. Information is made available to other IRB members who wish to review the project. The PI must submit the following materials to the HRPP office for continuing review:

5. Cover letter outlining the amendment request
6. Revised facesheet if there are changes to personnel, facilities or funding
7. Revised research plan, if applicable
8. Revised consent forms, if applicable
9. Additional information such as recruitment flyers, if applicable.

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.

All necessary information relevant to the assessment of the project's risks and benefits to study participants will be reviewed by the primary reviewer and an analyst assigned to the IRB committee.

Based on its review of the above information the IRB determines for each approved research protocol whether the research is re-approved, requires modifications to secure re-approval, is suspended or disapproved (terminated) based on assessment of the project's risks and benefits. 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.

### 3.12.3. Applicable Regulations

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

## 3.13. **Reporting Adverse Events and Unanticipated Events Involving Risks to Subjects or Others**

### 3.13.1. Policy

Federal regulations [45CFR46.103(b)(5) and 21CFR56.108(b)(1)] require the IRB to ensure that investigators promptly report “any unanticipated problems involving risk to subjects or others” (UPR). The IRB defines UPRs as any problem or event, which in the opinion of the Principal Investigator was: 1) unanticipated, 2) serious, AND 3) at least possibly related to the research procedures.

In addition, the US 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 research plan must have procedures for reporting unanticipated problems that involve risks to human subjects or others. The following events meet the IRB's definition of UPR and should be reported within 10 working days:

1. Any serious event (injuries, side effects, deaths or other problems), which in the opinion of the Principal Investigator was unanticipated, involved risk to subjects or others, and was possibly related to the research procedures.
2. Any serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk.
3. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
4. Any new information (e.g. publication, safety monitoring report, updated sponsor safety report), interim result or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
5. Any breach in confidentiality that may involve risk to the subject or others.
6. Any complaint of a subject that indicates an unanticipated risk or that cannot be resolved by the Principal Investigator.
7. The question of whether the event involved hospitalization, serious injury, or death is no longer of primary relevance in determining what should be reported.
8. If the event meets all criteria in the IRB's definition of UPRs, it must be reported to the IRB within 10 days.

PIs are encouraged to submit UPR reports using paper format. Hard copy submissions ensure that there is no information lost when uploading the report electronically and that the report can always be submitted over the PI's signature. Once the hard copy is received by the HRPP office, it will be scanned into the study file and made available to all relevant research oversight offices such as the Central Clinical Trials office, General Clinical Research Center, VASDHS, and Cancer Center depending upon the characteristics of the protocol.

The IRB will review unanticipated problems involving risks to participants or others (UPR) that include both minimal risk and more than minimal risk.

The IRB will have sufficient information to determine whether each reported problem represents a UPR. A range of some appropriate actions that may be considered by the IRB are listed, including revision of the protocol or informed consent forms, notification of subjects, re-consenting, or requiring changes in research procedures, suspension, or termination. The VA ACOS/R&D and RCO will also be informed of potential UPR or unexpected deaths so that an independent VA determination can be made.

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 UPR 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.

The IRB will determine whether each reported problem represents an unanticipated problem involving risks to subjects or others, an unexpected death, or an expected outcome based on the subjects medical history or the nature of the study as described in the protocol and informed consent. The IRB will determine appropriate actions for mitigating unexpected problems. 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. Other potential actions include revising the protocol and informed consent form for future subjects, requiring changes in study procedures, or suspending the study temporarily or permanently.

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, VA San Diego Healthcare System administration, in compliance with guidance provided by federal regulations and University policy. For VA research, the HRPP Director will report these determinations to the Associate Chief of Staff or Research and Development and the Research Compliance Officer.

### 3.13.2. Definitions.

1. Unanticipated (unexpected) problems/events are those that are *not* already described as potential risks in the consent form, *not* listed in the Investigator's Brochure or *not* part of an underlying disease. Anticipated (expected) problems/events do NOT meet the IRB's definition of UPRs.
2. Serious problems/events are those, which in the opinion of the Principal Investigator involve risk to subjects or others. Examples may include death, hospitalization, disability as well as breach of confidentiality. Non-serious problems/events do NOT meet the IRB's definition of UPRs.
3. A Serious Adverse Event is defined by the FDA as any adverse drug experience occurring at any dose that 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 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 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. FDA Federal Regulations require IND sponsors to report serious AEs via expedited reporting.

4. Problems/events that are unanticipated and serious should be reported to the IRB within 10 working days *only* if in the opinion of the Principal Investigator they are possibly, probably or definitely related to the research procedures. Those serious, unanticipated problems/events that the Principal Investigator deems unlikely or not related do NOT meet the IRB's definition of UPRs and need not to be reported to the IRB.

#### 3.13.2.1. Examples.

The following types of events are examples of unanticipated problems involving risks to participants or others that should be reported to the IRB:

- a. Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur.
- b. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject. See, Guidance on Changes to Eliminate Imminent Hazards.
- c. Any publication in the literature, data and safety monitoring report, interim result (e.g., suspension of enrollment due to new risk information) or other finding that indicates an unexpected change to the risk/benefit ratio of the research.
- d. Any breach in confidentiality or privacy that may involve risk to a participant or others.
- e. Any complaint of a subject that indicates an unanticipated risk (e.g., unexpected side effect) or that cannot be resolved by the research staff.
- f. Incarceration of a participant in the course of a study.
- g. A change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
- h. In FDA clinical trials, adverse events that are serious, unexpected, and reasonably related to the study treatment or intervention and that are expected to result in a change to the protocol or consent documents and/or dissemination of new information to subjects and any unanticipated adverse device effect occurring during the trial.
- i. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

3.13.2.2. IRB Review of Reports of Unanticipated Problems involving Risks to Participants

The IRB evaluates the report and determines whether the event constitutes an unanticipated problem. The IRB will also make a decision as to what the appropriate remedies should be, including whether research should be suspended or terminated, and whether the event needs to be reported to federal departments or agencies, such as Office of Human Research Protection (OHRP) or the Food and Drug Administration (FDA), the Institution, and VASDHS if appropriate.

3.13.2.3 Applicable Regulations

21 CFR 56.108

[Office for Human Research Protections \(OHRP\) Website.](#)

3.13.2.4 Procedures

Person(s) Responsible	Procedures
Principal Investigator	Submits AE and UPR reports in a timely fashion to the HRPP Develop research plan describing data and safety monitoring
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.

3.13.2.5 References, Forms, and Links

UCSD Adverse Event and UPR Report Form

**3.14. Protocol and Regulatory Violations**

3.14.1. Policy

3.14.1.1. 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.

3.14.1.2. Regulatory Violations

The IRB shall investigate allegations concerning possible non-compliance with these policies and all applicable federal, state, and institutional polices and regulations.

During such investigations, confidentiality will be maintained concerning the source of the report to the extent allowed by law.

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.

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. Director, HRPP will report noncompliance by VA investigators to ACOS/R&D and/or RCO.

3.14.2. Applicable Regulations

[45 CFR 46.112](#)

[45 CFR 46.113](#)

3.14.3. Procedures

Person(s) Responsible	Procedures
HRPP program staff	Respond to all inquiries and ‘whistleblower’ complaints promptly
IRB Administrator IRB Chairs or designee	Develop plan for and implement investigation of alleged noncompliance. Maintain documentary evidence of investigation Report findings to principal investigator, appropriate institutional officials, and outside agencies

### 3.15. **Radiation Exposure and Radioisotopes**

#### 3.15.1. Policy

All projects, including their amendments, 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.

#### 3.15.2. Applicable Regulations

[21 CFR 812.2\(b\)\(1\)\(ii\)](#)

[21 CFR 812.66](#)

[21CFR 56.108\(a\)\(1-2\)45 CFR](#)

[46.109](#)

[45 CFR 46.111](#)

3.15.3. 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

**3.16. Banking of Specimens**

3.16.1. 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.

3.16.1.1. 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.

#### 3.16.1.2. 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.

1. If research results of the reuse of the specimen will this be conveyed to the subject.
2. If the subject will be re-contacted after the original study is completed.

3. If the subject requests, the specimen and all links to the clinical data will be destroyed.
4. That refusal to participate does not affect the subject's ability to participate in any associated therapeutic research.
5. 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;
6. 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.
7. If the investigator has any commercial interest from which he/she may benefit financially, directly or indirectly.
8. 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.

#### 3.16.1.3. 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.

3.16.2. 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](#)

3.16.3. 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

### 3.17. Advertisements and Recruitment Materials

#### 3.17.1. 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.

The FDA considers direct advertisement for research participation to be the start of the informed consent process. 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:

1. Name and address of the clinical investigator;
2. Purpose of the research and summary of eligibility criteria;
3. Straightforward and truthful description of the benefits to the subject;
4. Location of the research and who to contact for information;
5. 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](http://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.

#### IRB Review of Advertisements

The IRB reviews “direct advertising for research participants,” which is defined as advertising that is intended to be seen or heard by prospective participants to solicit their participation in a study. When advertisements are easily compared to the approved consent document, the IRB chair, or other designated IRB member, may review and approve by expedited means. When the IRB reviewer has doubts or other complicating issues are involved, the advertising should be reviewed at a convened meeting of the IRB.

When the IRB evaluates the selection of participants, it considers the influence of payments to participants. IRB review and approval of listings of clinical trials on the Internet is not required when the system format limits the information provided to basic trial information, such as:

- 1 the title; purpose of the study;
- 2 protocol summary;
- 3 basic eligibility criteria;
- 4 study site location(s); and
- 5 how to contact the site for further information.

The IRB should review the information contained in the advertisement and the mode of its communication, to determine that the procedure for recruiting participants is not coercive. The IRB should review the final copy of printed advertisements to evaluate the relative size of type used and other visual effects. When advertisements are to be taped for broadcast, the IRB should review the final audio/video tape. The IRB may review and approve the wording of the advertisement prior to taping to preclude re-taping because of inappropriate wording. The review of the final taped message prepared from IRB - approved text may be accomplished through expedited procedures. IRBs should review advertising to assure that advertisements do not:

1. State or imply a certainty of favorable outcome or other benefits beyond what is outlined in the consent document and the protocol;
2. Make claims, either explicitly or implicitly, that the drug, biologic or device is safe or effective for the purposes under investigation;
3. Make claims, either explicitly or implicitly, that the test article is known to be equivalent or superior to any other drug, biologic or device;
4. Use terms such as “new treatment,” “new medication” or “new drug” without explaining that the test article is investigational;
5. Promise “free medical treatment,” when the intent is only to say participants will not be charged for taking part in the investigation.

Advertisements may state that participants will be paid, but should not emphasize the payment or the amount to be paid, by such means as larger or bold type. Advertisement to recruit participants should be limited to the information the prospective participants need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements.

The name and address of the clinical investigator or research facility;

The condition under study or the purpose of the research;

In summary form, the criteria that will be used to determine eligibility for the study;

A brief list of participation benefits, if any (e.g., a no-cost health examination);

The time or other commitment required of the participants; and

The location of the research and the person or office to contact for further information.

No advertisement can include any exculpatory language. [38 CFR §16.116] [45 CFR §46.116] [21 CFR §50.20]

3.17.1. Applicable Regulations

[45 CFR 46.301-306](#)

[21 CFR 56](#)

3.17.2. Procedures

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

**4. Functions and Operations**

**4.1. IRB Meetings**

4.1.1. 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.

4.1.1.1. 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 members. Once finalized, no one, including a higher authority, may make any changes in the final minutes except the IRB at a convened meeting. Draft minutes are also made available to the VASDHS R&D Committee for review at a subsequent meeting. The IRB Administrator will maintain copies of the minutes.

#### 4.1.1.2. Telephone Conference Call Meetings

Every effort will be made to convene meetings at which all members are present. However, should a member not be able to be physically present during a convened meeting, but is available by telephone, the meeting can be convened using teleconferencing methods. The member who is not physically present will be connected to the rest of the members via speakerphone or interactive audio and video connection. In this manner, all members will be able to discuss the protocol even though one member is not physically present. Members participating by conference call may vote; provided they have had an opportunity to review all the material the other members have reviewed.

No member who is absent from a convened meeting and is not participating in a teleconference may vote on an issue discussed during a convened meeting (no proxy written or telephone polling).

Rarely, in an emergency, meetings may be convened via a teleconferencing. A quorum (as defined above) must participate for the conference call meeting to be convened. To allow for appropriate discussion to take place, all members must be connected simultaneously for a conference call to take place -- "telephone polling" (where members are contacted individually) will not be accepted as a conference call.

#### 4.1.2. Applicable Regulations

[45 CFR 46.101\(a\)](#)  
[45 CFR 46.107 \(e\)](#)  
[45 CFR 46.108 \(b\)](#)  
[21 CFR 56.103\(a\)](#)  
[21 CFR 56.107\(e\)](#)

[21 CFR 56.108\(c\)](#)  
[38 CFR 16.101 \(a\)](#)  
[38 CFR 16.107 \(e\)](#)  
[38 CFR 16.108 \(b\)](#)  
[ICH 3.2-3.5](#)  
[VHA Handbook 1200.5](#)

#### 4.1.3. Procedures

Person(s) Responsible	Procedures
IRB Administrator IRB Chair	Schedule meetings
IRB Administrator IRB Staff	Distribute notice of meeting and all meeting materials
Primary and Secondary Reviewers	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

### 4.2. Categories of Action

#### 4.2.1. 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.

##### 4.2.1.1. Categories of Action

1.	<b>Approval</b>	Action taken if majority of committee votes for approval and no more than one dissenting vote is cast.
2.	<b>Approval Pending</b>	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.	<b>Deferral:</b>	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.
4.	<b>Disapproval:</b>	Action taken if two or more dissenting votes are cast that would not be altered by the proposed modifications.

#### 4.2.1.2. 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 re-approve 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.

#### 4.2.1.3. 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.

For VA studies, the IRB will ensure that the study file maintained by the HRPP includes all correspondence between the IRBs and the Research and Development Committee, any unexpected adverse events submitted to the IRB and any protocol violations submitted to the IRB. Information retained by the IRB includes:

- (1) Copies of all items reviewed, including, but not limited to: research proposals, investigators' brochures and recruitment materials; scientific evaluations (if any) that accompany the proposals; approved consent documents; approved HIPAA Authorization document, if separate from the informed consent, any proposed amendments and the IRB action on each amendment; progress reports submitted by investigators; reports of injuries to subjects and serious and unexpected adverse events; documentation of protocol violations; and documentation of non-compliance with applicable regulations
- (2) Records of continuing review activities.
- (3) Copies of all correspondence between the IRB, investigators, and the R&D Committee
- (4) Statements of significant new findings provided to subjects (as required by App. C) must be maintained with the related research proposal and, when reviewed at an IRB meeting, must be documented in the minutes.
- (5) For initial and continuing research review by the expedited procedure: The specific permissible category.
- (6) Description of actions taken by the reviewer.
- (7) Any findings required under the regulations.
- (8) Determinations required by the regulations and protocol-specific findings supporting those determinations for research involving children.
- (9) For each protocol's initial and continuing review, the frequency for the next continuing review.

#### 4.2.2. Applicable Regulations

[21 CFR 56.110\(b\)](#)  
[21 CFR 56.111](#)  
[45 CFR 46.110\(b\)](#)  
[45 CFR 46.111](#)  
[38 CFR 16.110 \(b\)](#)

[38 CFR 16.111](#)  
[ICH 3.1.1](#)  
[ICH 3.3.9](#)  
[VHA Directive 2001-028](#)

#### 4.2.3. 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.

### **5. Protocol Audits and Scientific Misconduct**

#### **5.1. Protocol Audits**

##### 5.1.1. 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:

1. an allegation of or evidence suggesting noncompliance with applicable regulations or institutional policies
2. noncompliance with policies of the IRB as outlined in this document
3. expressed concerns by the sponsor regarding the investigator’s work

4. a complaint by a subject in a study about protocol or subject's rights violations
5. a potential high risk to subjects
6. recruitment of vulnerable populations
7. studies that involve large numbers of subjects
8. investigators who are conducting multiple studies under IRB jurisdiction
9. research by an investigator outside of their specialty areas
10. safety or effectiveness findings that are inconsistent with other investigators studying the same test article
11. too many subjects with a specific disease given the locale of the investigation are claimed
12. laboratory results that are outside the range of expected biological variation
13. studies selected at the discretion of the IRB
14. an allegation of or evidence suggesting abuse of research subjects
15. an allegation of or evidence suggesting scientific misconduct
16. associated with unexpected serious harm to participants

#### 5.1.1.1. 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.

#### 5.1.1.2. 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

#### 5.1.2. Applicable Regulations

[45 CFR 46.103 \(b\)\(4\)\(ii\)](#)  
[38 CFR 16.109\(e\)](#)  
[38 CFR 16.103\(b\) \(4\)\(ii\)](#)

[21 CFR 56.108\(a\)\(2\)](#)  
[21 CFR 56.109 \(f\)](#)  
[45 CFR 46.109\(e\)](#) [VHA Handbook 1200.5](#)

### 5.1.3. Procedures

Person(s) Responsible	Procedures
IRB Administrator	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. Provide audit with Audit Checklist Contact Investigator to arrange audit logistics.
Auditors	Review all documents that could provide factual information regarding conduct of the study. 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. Confirm information about any adverse events that may have been reported. Obtain information about any adverse events that may not have been reported. Confirm status of project (enrolling, inactive etc) Complete Audit Report within 10 working days of completing the audit.
IRB Members	Review Audit Report Assess the need for additional information. Determine audit conclusion. Vote on remedial action imposed on investigator, as necessary.

### 5.1.4. References and Forms

UCSD On Site Audit Checklist; FDA GCP Audit Guidelines

## **5.2. Communications, Sanctions, Appeals and Disciplinary Actions**

### **5.2.1. 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.

#### **5.2.1.1 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. For VA research, the Chair or designee will use the VASDHS definitions to determine whether an incident should be considered minor, serious, or continuing noncompliance. The HRPP Director will immediately inform the VA ACOS/R&D of any incident that appears to meet the VA definition of serious or continuing noncompliance.

#### **5.2.1.2. Minor Noncompliance:**

Minor noncompliance 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, rights, or welfare. 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 continuing noncompliance.

#### **5.2.1.3. 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 significant 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. For VASDHS research, serious noncompliance refers to noncompliance that resulted in an increased risk to subjects or adversely affects the rights or welfare of subjects.

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 Chair and HRPP Director will provide members with sufficient information to review noncompliance, which may include an investigator audit if necessary. Generally, all materials relevant to a review of noncompliance would be provided on the HRPP database. 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, VACO for VA-related research, and the institution employing the investigator. In addition, Director of the HRPP shall report VA-related instances of noncompliance to ACOS/R&D and or RCO.

In the event that a project is suspended or terminated, the IRB will request from the PI written documentation on how the safety and well-being of subjects currently enrolled in the project will be protected. Unless otherwise stated, a suspended project must cease enrollment of new participants until the suspension is lifted. Currently enrolled subjects may continue to be followed if necessary to ensure subject safety.

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.

#### 5.2.2. 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. For VASDHS studies, the VA ACOS/R&D will also be notified by memo or email as soon as possible.

When study approval was suspended or terminated, the convened IRBs or IRB chairs considered actions to protect the rights and welfare of currently enrolled participants. The IRBs must notify investigators to submit immediately to the IRB chair, a list of participants for whom stopping research activities would cause harm, if applicable. Upon IRB Chair approval (and for VA studies, in consultation with the Chief of Staff), the IRB may allow current participants to continue interventions or interactions if the IRB finds an over-riding safety concern or ethical issue involved such that it is in the best interests of individual participants to continue participating.

The IRBs should consider whether procedures for withdrawal of enrolled participant took into account their rights and welfare. IRBs need to consider whether the PI must inform current participants of the termination or suspension. Upon suspension or termination of IRB approval, the PI is required to report to the IRB updated information on any adverse

events or outcomes that have not been previously reported. For VASDHS studies, The HRPP Director will submit a report to the ACOS/R&D in accordance with VA MCM 151-10, "Human Research Reporting Requirements".

### 5.2.3. Expired, Suspended or Terminated Protocols

The HRPP is responsible for promptly notifying the PI when a study has expired, I suspended or is terminated. The sponsoring agency, private sponsor, or other Federal agencies (including the ORD and ORO in the case of a VA study) must also be informed. The PI, not the IRB, is responsible for reporting expired, suspended, or terminated protocols to the sponsor.

### 5.2.4. Scientific and Research Misconduct

Scientific misconduct is defined as fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results (see Appendix for definitions). 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, for VA Research to the VA ACOS for Research, to pursue according to institutional and University policies. Scientific misconduct on the part of a VA investigator should be reported to the VA Research Integrity Officer.

Research misconduct means fabrication, falsification, or plagiarism in proposing, performing, or reviewing research, or in reporting research results. (a) Fabrication is making up data or results and recording or reporting them. (b) Falsification is manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record. (c) Plagiarism is the appropriation of another person's ideas, processes, results, or words without giving appropriate credit. (d) Research misconduct does not include honest error or differences of opinion.

### 5.2.5. 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.

### 5.2.6. Applicable Regulation

5.2.7. 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.

**6. e-IRB Electronic Submission and Review**

6.1. 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.

6.2. Applicable Regulations

[21 CFR 11 subpart C](#)

6.3. Procedures

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

#### 6.4. References, Forms, and Links

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

### 7. **Multi-site Studies**

#### 7.1. Policy

It is the policy of this Institution to assure that all facilities participating in a human subjects study receive adequate documentation about the study in order to protect the interests of study participants. Before a study can begin, it must be approved by the IRB of record for the coordinating facility, the IRBs of record for each participating facility, and, for VA research, applicable Research and Development (R&D) Committees.

#### 7.2. Procedures

##### 7.2.1. Investigator Responsibilities - Coordinating Facility

If UCSD or the VA is the coordinating facility, the PI must document how the important human subject protection information will be communicated to the other participating facilities engaged in the research study. The investigator is responsible for serving as the single liaison with outside regulatory agencies, with other participating facilities and for all aspects of internal review and oversight procedures. The PI is responsible for obtaining IRB review and approval from the coordinating facility's IRB of record and for ensuring that all participating facilities obtain review and approval from their IRB of record. The PI is responsible for notifying each participating facility that the coordinating facility is engaged in multi-site research involving the participating facility. This documentation must include all relevant contact information.

When the investigator is the lead investigator of a multi-site study, the application must include information about the management of information relevant to the protection of participants, such as unanticipated problems involving risks to participants or others, interim results, and protocol modifications.

##### 7.2.2. Investigator Responsibilities - Participating Facilities

The Investigator has the overall responsibility for the conduct of the study at the participating facility.

##### 7.2.3. IRB Responsibilities

In cases where an agreement exists (for example, a Memorandum of Understanding, MOU) between the coordinating and participating facilities, the Investigator must provide

documentation to the IRB of the coordinating facility of his/her intent to rely on the coordinating facility's IRB of record for ethical, scientific, and regulatory review and approval. In these cases, the participating facility's IRB of record is considered the "relying IRB", whereas, the coordinating facility's IRB of record is considered the "reviewing IRB". The study cannot be initiated without approval from both the relying and reviewing IRB. The IRBs of record for the coordinating and participating facilities must maintain records of approval and notices of intent to rely and documentation that the requirements of the MOU have been followed.

#### 7.2.4. External (Off-Site) Adverse Event Reporting

As part of ongoing monitoring of safety in multi-site trials, external (off-site safety reports) are provided to PIs. The institution is in agreement with OHRP's assessment that these reports of individual external adverse events often lack sufficient information to allow investigators or IRBs at each institution engaged in a multicenter clinical trial to make meaningful judgments about whether the adverse events are unexpected, are related or possibly related to participation in the research, or suggest that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized. In general, the investigators and IRBs at external institutions are not appropriately situated to assess the significance of individual external adverse events. Ideally, adverse events occurring in subjects enrolled in a multicenter study should be submitted for review and analysis to a monitoring entity (e.g., the research sponsor, a coordinating or statistical center, or a DSMB/DMC) in accordance with a monitoring plan described in the IRB-approved protocol.

Only when a particular adverse event or series of adverse events is determined to meet the criteria for an unanticipated problem should a report of the adverse event(s) be submitted to the IRB at each institution under the HHS regulations at 45 CFR part 46.

It will be the policy of this Institution to handle these external adverse event reports as follows:

- 1) The local PI serves as the recipient of the external (off-site) reports. The PI must provide a summary report to the IRB that includes:
  - a) a clear explanation of why the adverse event or series of adverse events has been determined to be an unanticipated problem. (Do any of the events described in these reports constitute UPRs?)
  - b) the investigator should review the report and assess whether it identifies the adverse event as being: (1) unexpected; (2) related or possibly related to participation in the research; and (3) serious or otherwise one that suggests that the research places subjects or others at a greater risk of physical or psychological harm than was previously known or recognized.
  - c) A description of any proposed protocol changes or other corrective actions to be taken by the investigators in response to the unanticipated problem

should be described. (For example, whether these reports require any modifications to approved recruitment materials, consent forms, or research plans.)

- 2) The HRPP office will not send notification to the PI that these reports were received.
- 3) The PI is required to maintain reports as agreed upon with the sponsor and following institutional policy.

## 8. Appendix

### 8.1. Abbreviations

ACOS	Acting Chief of Staff (VA)
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
OCCA	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
RCO	Research Compliance Office (VA)
SAE	Serious Adverse Event
SOM	School of Medicine
SOPP	Standard Operating Policies and Procedures
UCSD	University of California, San Diego
UPR	Unanticipated Problem Involving Risk to Subjects or Others
VASDHS	Veteran Affairs, San Diego Healthcare System
VMRF	Veterans Medical Research Foundation

## 8.2. 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.

**Fabrication:** the making up of data or results and recording or reporting them.

**Falsification:** manipulating research materials, equipment, or processes, or changing or omitting data or results such that the research is not accurately represented in the research record.

**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:** as defined by DHHS regulations means 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. [45 CFR 46.102(f)]. As defined by FDA regulations, “human subject” means an individual who is or becomes a subject 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 50.3(g), 21 CFR 56.102(e)] A human subject includes an individual on whose specimen a medical device is used. [21 CFR 812.3(p)]

**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 information:** As defined by DHHS, means information that is individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information).

**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:** As defined by DHHS regulations, means communication or interpersonal contact between investigator and subject. [45 CFR 46.102(f)]

**Intervention:** As defined by DHHS regulations, means 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. [45 CFR 46.102(f)]

**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)

**Plagiarism:** the appropriation of another person's ideas, processes, results, or words without giving appropriate credit.

**Private Information:** As defined by DHHS regulations, means information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (for example, a medical record) [45 CFR 46.102(f)]. 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:** As defined by DHHS regulations means a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge. [45 CFR 46.102(d)]. As defined by FDA regulations means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) or 520(g) of the Federal Food, Drug, and Cosmetic Act, or need not meet the requirements for prior submission to the Food and Drug Administration under these sections of the Federal Food, Drug, and Cosmetic Act, but the results of which are intended to be later submitted to, or held for inspection by, the Food and Drug Administration as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, study, and clinical investigation are synonymous for purposes of FDA regulations [21 CFR 50.3(c), 21 CFR 56.102(c)].

Research includes:

1. Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 505(i) of the Federal Food, Drug, and Cosmetic Act” means any use of a drug other than the use of an approved drug in the course of medical practice. [21 CFR 312.3(b)]
2. Experiments that must meet the requirements for prior submission to the Food and Drug Administration under section 520(g) of the Federal Food, Drug, and Cosmetic Act” means any activity that evaluates the safety or effectiveness of a medical device. [21 CFR 812.2(a)]

3. Any activity in which results are being submitted to or held for inspection by FDA as part of an application for a research or marketing permit is considered to be FDA-regulated research. [21 CFR 50.3(c), 21 CFR 56.102(c)]

**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)

**Unanticipated 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. "Unanticipated" 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).

**Unanticipated Problems Involving Risks to Participants:** An “unanticipated problem involving risks to participants or others” are events that: negatively affect the risk and benefit ratio of the research, were unanticipated by the investigator at the time the research was approved, and are more likely than not related to the research study.

**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 (“anonymized”) 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).

## 9. Change Summary

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

- d) 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.
- e) Replaced references to VHA Manual M-3, Part 1, Chapter 9 with references to VHA Handbook 1200.5, throughout document.
- f) 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).
- g) 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.
- h) 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.
- i) 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.

2/4/2007 changes relative to version date 5/28/2004

- 1 Reformatted document using section and subsection numbers for more efficient cross-reference.
- 2 Updated text for AAHRPP compliance
- 3 Expanded policies on reporting unanticipated problems involving risk to participants (section 3.13.1.1.)
- 4 Add policy on Multi-site studies (section 7)

1/30/2008 relative to version date 2/4/2007

- 1 Multiple and significant revisions based on AAHRPP Site Visit, Response to the Site Visit Draft Report, and Improvement Plan.
- 2 Corrected several numbering and formatting errors
- 3 Updated AE and UPR policy, including off-site (external) SAEs
- 4 Revised policy on unplanned emergency use of an investigational agent
- 5 Updated definitions of “human subject”, “research”, and others based on DHHS definitions