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

Section 1.1
Responsibility and Authority

Policy

In accordance with federal policy on the Protection of Human Subjects (DHHS Policy 45 CFR Part 46, FDA Policy 21 CFR Parts 50 and 56), the University of California, San Diego (UCSD) is responsible for the protection of the rights and welfare of human subjects in research conducted by, or under the supervision of, UCSD faculty, staff or students. To conduct this responsibility effectively, the University supports Institutional Review Board (IRB) Committees that provide initial review and ongoing review and oversight of the ethical conduct and subject health and welfare for 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.

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

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. Require applications for study re-approval from investigators.
4. Oversee conduct of the study.
5. Observe or have a third party observe the consent process and the conduct of the research.
6. Suspend or terminate a study.
7. Place restrictions on a study.

In compliance with 45 CFR 46.112, research that has been approved by an IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB. Further, the institution, its officials, or other institutional committees may not override an IRB decision to disapprove a study. These policies and procedures apply to research involving human subjects conducted by UCSD faculty, staff, and students for research conducted completely or partially at UCSD, 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 Human Research Protections Program (HRPP) to review their human subjects research.

The IRB functions 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.

Members of UCSD IRBs and HRPP administration/staff are encouraged to report any attempt to use or use of undue influence in the performance of their duties. "Undue influence" means attempting to interfere with the normal functioning and decision-making of the IRB or to influence an IRB member or HRPP administration/staff outside the established processes or normal accepted methods, in order to obtain a particular result, decision or action by the IRB or HRPP. Report of an attempt to use or use of undue influence should be made to the IRB Chair, Director of the HRPP, or UCSD Institutional Official (IO) for Human Research. The report may also be made using the UCOP Whistleblower Policy (http://www.ucop.edu/uc-whistleblower/). The IRB Chair, HRPP Director, IO and/or designated official will investigate the allegations and take appropriate actions including informing the IRB for review of allegations and possible suspension of research privileges.

To help preclude undue influence of IRB members, the HRPP preserves the anonymity of members. A list of IRB members that includes gender, scientist/non-scientist, primary scientific/non-scientific specialty, and institute affiliation is on file with the U.S. Department of Health and Human Services.

Section 103(a) of 45 CRF 46 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), 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, unless the research has been determined to be exempt from IRB review or the UCSD IRB has entered into an agreement with an "outside" IRB or non-UCSD institution to provide review such as a Review/Rely agreement.

The University of California, San Diego has five IRBs 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. Each of these IRBs has been established in accordance with the requirements of applicable federal rules. DHHS Registration numbers for the five IRBs include the following:

Committee A: IRB00000354
Committee B: IRB00000353
Committee C: IRB00002758
Committee D: IRB00005945
Committee S: IRB00000355

Procedures

1. UCSD Institutional Official
    a) Authorize and sign FWA
    b) Ensure ongoing authority of IRB to perform its function
    c) Investigate allegations of undue influence and take appropriate action(s)
2. HRPP Director
    a) Retain file copy of institutional FWA
    b) Investigate allegations of undue influence and take appropriate action(s)
3. IRB Chair
    a) Investigate allegations of undue influence and take appropriate action(s)

Applicable Regulations

21 CFR 50.20
21 CFR 56.109(a, f)
21 CFR 56.112
21 CFR 56.113
21 CFR 312.2
21 CFR Subpart D
21 CFR 312.80 to 88
45 CFR 46.101
45 CFR 46.109(a, e)
45 CFR 46.112
45 CFR 46.113
The Belmont Report
California Health and Safety Code 24170-24179.5

References Forms and Links

Federalwide Assurance, FWA0004495, available from HRPP office.
https://irb.ucsd.edu/about.shtml
http://ohrp.cit.nih.gov/search/search.aspx (use IORG number 0000210)

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

Section 1.2
HRPP Program Organization

Policy

The Dean's Office, UCSD School of Medicine, supports the UCSD Human Research Protections Program (HRPP) 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 (R&D) 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 Vice Chancellor for Health Sciences and Institutional Official for matters involving UCSD IRB policy and institutional compliance. There is an Assistant Director who has operational management responsibilities within the program and report to the Director. This Assistant Director has personnel management responsibilities for protocol analysts within the HRPP office, and administrative support staff.

Procedures

1. IRB Director
    a) Program interactions with VASDHS, Vice Chancellor for Health Sciences, and Institutional Official.
    b) Policy and procedure development consistent with federal and local organizational requirements.

c) Oversight of program implementation and management

2. IRB Associate Directors
    a) Policy and procedure development in collaboration with IRB Administrator
    b) Overall program implementation and management
    c) Office personnel management

Applicable Regulations

21 CFR 56.101(a)
21 CFR 56 109
21 CFR 56.113
38 CFR 16.101
38 CFR 16.109(a,e)
38 CFR 16.113
45 CFR 46.101
45 CFR 46.109
45 CFR 46.113

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

Section 1.3
Review and Updating of SOPPs

Policy

The Standard Operating Policy and Procedures (SOPPs) of the Institutional Review Boards must remain current and in compliance with all applicable regulations. To remain current, the SOPPs are reviewed and periodically updated. The review process will update these policies and procedures to comply with the most recent federal, state, University of California, and UCSD regulations. This review will be documented. Notifications of changes and an updated SOPP will be made available to members of the IRBs, HRPP staff, as appropriate, and posted on the HRPP website at https://irb.ucsd.edu.

Procedures

1. Steering Committee
    a) Review the SOPPs as needed, as determined by an IRB Chair, members of the Steering Committee, the IRB Director, an IRB Associate Director, and/or a majority of the IRB members.
    b) Document the review and updating of SOPP(s) by including a revision date on the SOPP and a synopsis of revisions made to the SOPP on the HRPP website.
2. IRB Chairs and IRB Director
    a) Review and approve each SOPP. Approval of an SOPP is documented by either signature, electronic signature, or e-mail from each IRB Chair and IRB Director specifically noting the SOPP(s) that has/have been approved or by using the following procedures:
        1. The IRB Chairs and IRB Director as well as the other members of the Steering Committee are provided with a revised/new SOPP for review and approval.
        2. The Committee has 14 days for review and to request any revisions.
        3. If no request(s) for revision(s) is/are provided within 14 days after the revised/new SOPP has been provided to the Steering Committee, the SOPP is approved.
        4. If request(s) for revision is/are provided, the SOPP will be revised, and the revised SOPP will be provided to the IRB Chairs and IRB Director.
        5. If no request(s) for revision(s) is/are provided within 7 days after the revised SOPP has been provided to the IRB Chairs and IRB Director, the SOPP is approved.

6. If any request(s) for revision(s) is/are provided during the 7 day period, the SOPP will reviewed at the next Steering Committee meeting.
7. At any time during the review of a revised/new SOPP, any Steering Committee member may request that the revised SOPP be reviewed at the next Steering Committee meeting.

An SOPP becomes effective once approval has been obtained, and the SOPP has been posted on the HRPP website.

3. IRB Members
    a) Review and discuss changes made in SOPPs.
4. IRB Director
    a) Retain file copies of current and archive copies of previous SOPPs.
    b) Inform IRB members of changes made to SOPPs.
5. HRPP Web Editor
    a) Create readable/downloadable versions of SOPPs for access by IRB Chairs, IRB members, HRPP staff as well as the research community at large.
    b) Update the HRPP website to post the revised SOPP and a synopsis of the revision(s) made to each SOPP.

Applicable Regulations

21 CFR 56.108(a)
21 CFR 56.115 (6)
45 CFR 46.103 (b) (4)
45 CFR 46.108 (a)
45 CFR 46.115 (6)

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

Section 1.4
Documentation and Records Retention

Policy

The Institutional Review Board (IRB) Director or his/her designee will prepare and maintain adequate documentation of IRB/Human Research Protections Program (HRPP) activities, including the following:

1. Copies of all original research proposals reviewed; scientific evaluations, if any, that accompany the proposals; investigator brochure, if any; approved consent/permission/assent documents, if any; recruitment materials; applications for study re-approval; study progress reports and interim reports; modifications; adverse event report forms submitted by investigators; documentation of non-compliance; reports of injuries to subjects; and other reports, such as data and safety monitoring reports, unanticipated problems involving risks to participants or others, case histories, if requested, submitted to the studies.
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) Information and advisement of expedited review activity since the last IRB meeting.
    g) Actions taken by the IRB.
    h) Separate deliberations for each action.
    i) The vote on actions including the number of members voting for, against, and abstaining.
    j) That the informed consent document was reviewed in accordance with applicable criteria and contains all of the required elements if the study is approved. If not approved, a description of the missing elements.
    k) The justification for waiving any or all of the required elements of informed consent.
    l) A determination of risk level of investigational devices.
    m) 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.

n) The basis for requiring changes in or disapproving research.
o) A written summary of the discussion of controverted issues and their resolution.
p) Review of additional safeguards to protect vulnerable populations if entered as study subjects.
q) The frequency of continuing review of each proposal as determined by the IRB.
r) Any significant protocol-specific finding that may alter risk/benefit ratio.
s) Decisions regarding privacy including use or disclosure of protected health information, including HIPAA decisions.
t) Any significant new finding provided to participant, if reviewed by the IRB.
u) Justification for any deletion or substantive modification of information concerning risks or alternative procedures contained in the DHHS-approved sample consent document associated with DHHS multi-site studies such as cooperative oncology trials, cardiology trials, and behavioral studies..
v) The approval period for initial and continuing review.

3. Copies of draft minutes available to regulatory agencies, VA Research and Development (R&D) Committee and members of internal and external audit teams, as requested, for reviewing IRB deliberations and decisions regarding UPRs and non-compliance. The IRB 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 unless “reapproval” is granted by the appropriate IRB, such as if substantive errors are found upon review of approved minutes. Corrections may be made to the minutes, and the “revised” minutes will be provided to the appropriate IRB for review and “reapproval.” 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. For initial and continuing review of research reviewed using expedited procedure, the specific permissible category, description of action taken by the reviewer, and any findings required under the regulations.
6. Copies of documentation associated with the justification for exemption determinations.
7. Copies of all correspondence between the IRB and the investigators.
8. 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).

9. Copies of SOPPs.
10. Statements of significant new findings provided to subjects.
11. Reports of any complaints received by subjects.
12. Access to current conflict of interest statements from IRB members.
13. Training for IRB members and staff.
14. Copies of informed consent/assent documents.
15. HIPAA authorization forms.

IRB records for a protocol are organized to allow a reconstruction of a complete history of IRB actions related to the review and approval of the research protocol.

Consistent with resources available, the UCSD HRPP will attempt to maintain records indefinitely wherever possible. At a minimum, IRB records will be retained for three years after completion of the research at the site or sites over which the IRB has jurisdiction for the study. In addition in accordance with VA requirements, if a protocol is cancelled without subject enrollment, IRB records are maintained for at least five years after cancellation. Records will be retained longer if required by applicable FDA, DHHS University of California, and UCSD 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 IRB Director, IRB Assistant Directors, and the IRB 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.

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.

Procedures

1. IRB Director, IRB Assistant Directors or designated HRPP staff
    a) Maintain full and complete files for all research studies.
    b) Maintain roster of regular and alternate IRB members.
    c) Establish archive method for files that are not in current use but must still be retained.

d) Establish technical and administrative procedures for maintenance of and access to physical and electronic records systems.

Applicable Regulations

21 CFR 56.103(a)
21 CFR 56.108(a-b)
21 CFR 56.115
45 CFR 46.103 (b)(4-5)
45 CFR 46.108 (a)
45 CFR 46.115
ICH 3.2.2

References, Forms and Links

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

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

Section 1.5
UCSD Institutional Policies

Policy

There are a number of local institutional policies that complement federal and state regulations regarding research involving human volunteers. In general UCSD 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 policy.

It is the policy of UCSD that only Principal Investigator-qualified faculty, as defined by UCSD policy PPM-150-10, can serve as the Principal Investigator (PI) on a study unless a PI exemption has obtained from the Office of Academic Affairs for funded studies. This policy, however, does not prohibit salaried faculty from submitting an application to the IRB with the non-salaried faculty as a co-investigator. Individuals who are non-faculty may be permitted to serve as a PI only for non-funded studies on a case-by-case basis. Circumstances under which this may be permitted include that the PI is affiliated with UCSD as a student or has a salaried appointment. The proposed PI must have appropriate training, resources, and qualifications to ensure the protection of the rights and welfare of individuals associated with the study. Student PIs will require a faculty supervisor to be a co-investigator on the study.

All clinical trials and other human subject activity that is not exempt from IRB review involving University faculty, staff, and students must be reviewed by a UCSD IRB unless UCSD has entered into an agreement with an "outside" IRB to provide review such as a Review/Rely agreement. 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, or UCSD Office of Clinical Trials Administration.

All sponsored clinical trials must have a clinical trial agreement in place, signed by one of the officials authorized to execute UCSD contracts and grants, before initiation of the clinical trial activity.

A copy of all FDA, NIH, Departmental, Divisional, Organizational Research Units, or Center audits and/or letters of warning must be forwarded to the HRPP Office within ten 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 HRPP Office prior to or immediately following 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 review of the safe use of hazardous biological materials and organisms, the use of radioactive materials or radiation-producing equipment that results in exposure to human subjects, and for the identification and management of conflict of interest issues of all investigators.

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.

Procedures

1. IRB Chair, IRB members and Chair Designees review Research Plan and consent documents for compliance with local institutional policy.

Applicable Regulations

Moore v. Regents of University of California, 51 Cal.3d 120, Supreme Court of California, July 9, 1990

PPM 150-10 Policy — Eligibility To Submit Proposals For Extramural Support

UCSD HRPP Standard Operating Policies and Procedures, section 3.19, Collaboration with UCSD Committees

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

Section 2.1
Composition of IRBs

Policy

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

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, and who is not part of the immediate family of a person who is affiliated with UCSD. 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.

In general, at least one unaffiliated member will be present at 10 out of 12 IRB meetings per year.

In general, at least one member who represents the general perspective of subjects will be present at 10 out of 12 IRB meetings per year.

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/or an Associate Director of the Human Research Protections Program will be voting/alternate members of one or more IRBs, so that each IRB has a representative of the senior management staff of the HRPP.

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 or at least five members in attendance, whether in person or by phone/video conference, whichever is greater. 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.

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.

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.

Procedures

Characteristics of members, including appointment term, committee assignment, departmental affiliation, and professional expertise, are maintained in the HRPP database system. In addition, curriculums vita 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.

1. IRB Chairs and IRB Administrator maintain a roster of all regular and alternate members for inspection purposes; a file on all members, to include their curriculum vita, letters of nomination and other evidence of professional ability; and a roster of available consultants who are eligible and qualified to attend meetings as invited consultants.
2. IRB Administrator and HRPP designated staff maintain a roster of all regular and alternate members for inspection purposes; a file on all members, to include their curriculum vita, letters of nomination and other evidence of professional ability; and a roster of available consultants who are eligible and qualified to attend meetings as invited consultants.

Applicable Regulations

21 CFR 56.107 (a-d, f)
21 CFR 56.115 (a)(5)
45 CFR 46.103 (b) (3)
45 CFR 46.107 (a-d, f)
45 CFR 46.115(a) (5)
ICH 3.2.1
ICH 3.2.6

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

Section 2.2
Member Appointment, Compensation, and Responsibilities

Policy

The UCSD-designated Institutional Official for Human Subjects Protection (i.e., FWA signatory), who is accountable for the HRPP, in consultation with the current IRB Chairs, the Director of the HRPP, and a majority of the IRB members on the IRB to which the Chair will be appointed, appoints a Chair for each IRB.

The Chair should have at least 1 year of experience as a regular IRB member. Typically, the Chair's experience would be with the Committee to which he/she is appointed. The Chair is appointed for 5 years and may be re-appointed based on their concurrence and that of the Institutional Official and the majority of the Chair's Committee.

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 federal, state, local, University of California, and/or UCSD IRB/HRPP standard operating policies and procedures and guidelines. The Chair may delegate any of his/her responsibilities, as appropriate, to other qualified and duly appointed members of the IRB including the IRB Vice-Chair.

A Vice-Chair will be appointed to each IRB. The Vice-Chair will be nominated by the IRB Chair and will be approved by a majority of the IRB member on the IRB to which the Vice-Chair will be appointed. The Vice-Chair is appointed for 5 years and may be re-appointed based on their concurrence of the IRB Chair and the majority of the Vice-Chair's Committee. The Vice-Chair may assume all the responsibilities of the Chair when so designated by the IRB Chair, as noted above.

IRB members will be selected in accordance with applicable UCSD policies on committee service. The selection of members and confirmation of alternates will be conducted by the IRB at a convened meeting by majority vote.

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.

A member may resign before the conclusion of his/her term. The vacancy will be filled as quickly as possible. Performance standards apply to IRB 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 the Chair of the Committee in consultation with the Director of the HRPP. The Chair may be removed from that position by a two-thirds vote of the full membership of the Chair's Committee at a convened meeting. When unexpected vacancies occur, an alternate member may be selected to fill the vacancy.

IRB senior staff, including the Director and Associate Directors, will have training and experience appropriate to their management responsibilities and competencies including 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 of the IRB Director, Associate Director and other IRB staff occur on an annual basis in accordance with institutional policies. In compliance with institutional employment policy, the evaluations are maintained within Human Resources under the jurisdiction of the Dean's Office, School of Medicine.

The IRB Chairs will be evaluated biannually assessment based on 5 criteria: 1) leadership, 2) participation, 3) technical knowledge, 4) teamwork, and 5) communication. The evaluation will be done by the members of the each Chair's IRB. This information will be maintained by the Institutional Official or designee, who will also provide formal feedback of the evaluation to the Chair.

The IRB members will be evaluated every three years by both the Chair of their Committee and the HRPP Director. The Chair or the HRPP Director will provide formal feedback of this evaluation.

The membership of each IRB will be periodically evaluated, and if necessary, adjusts to the membership and composition of the IRB to meet regulatory and organizational requirements will be made.

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 IORG through the Office of Human Research Protections database.

IRB Chair Responsibilities

1. Chairs convened meetings.
2. Monitor quorum at meetings.
3. Call special meetings when necessary.
4. Make decisions in emergency situations to protect subjects and remain in compliance with regulations.
5. Confirms primary and secondary reviewer assignments made by HRPP staff as requested.
6. Personally reviews or designates IRB member(s) to review SAEs and IND Safety Reports and determines which ones require review by the full board.

7. Personally determines or designates IRB member(s) to determine whether studies qualify for expedited review.
8. Performs or delegates review of applications and revisions meeting expedited review criteria.
9. Personally reviews or designates IRB member(s) to review all submitted investigator reports and determines if there is reason for full IRB review.
10. Reviews policies, procedures and forms on an ongoing basis.
11. Relates concerns of IRB staff and members to administration regarding issues in human research review.
12. Acts as an advisor and educator in the institution's research community.

IRB Members

1. Review research applications and other appropriate materials prior to convened meetings.
2. Provide sufficient advance notice if unable to attend a meeting.
3. Attend convened meetings and contribute to Board discussion.
4. Review studies according to approval criteria offered in the regulations and SOPP.
5. Serve as primary, secondary reviewer or discussant on selected applications.
6. Disclose any potential conflict of interest to the IRB chair as soon as it is recognized.
7. Maintain confidentiality regarding any information contained in any review.
8. Participate in project audits as needed.
9. Review policies, procedures and forms on an annual basis.
10. Understand these operating procedures and applicable federal, agency-specific and institutional regulations regarding human subjects research.

HRPP Program Director/IRB Administrator

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

HRPP Administrative Staff

1. Maintain up-to-date knowledge of policies, procedures and regulations regarding human subjects research and IRB operations.
2. Perform administrative duties to assure systematic flow of work through the IRB.
3. Prepare and distribute review materials to members and consultants.
4. Maintain files.
5. Prepare minutes.
6. Assure accurate and timely documentation, data input, and database up-keep.

7. Send out notification of IRB decisions, requests for additional information, and correspondence to investigators in a timely manner.
8. Send out timely reminders and notification to investigators when applications for study re-approval are due.

Compensation

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

1. IRB Chairs receive a $15,000 annual stipend.
2. Community Representatives receive $150 per IRB meeting attended.
3. Prisoner Advocates receive $150 per IRB meeting attended.
3. IRB members receive no direct payment; however, members are eligible to receive a laptop computer and an annual $500 Internet connection subsidy to offset costs of DSL or cable modem service. IRB members will be allowed to use the laptop computer for the duration of their tenure and to obtain replacement computers when deemed necessary. IRB members may request replacement or upgrade of the laptop computers as needed. All upgrade requests will be subject to available HRPP funds. All laptop computers remain property of the UC Regents. IRB members who leave IRB service are required to return the notebook computer to the HRPP.

Procedures

1. IRB Chairs and IRB members solicit regular and alternate IRB members from within and outside the institution, and the local community, following an appropriate schedule; follow established criteria to select new members; and replace members who resign or leave IRB service.
2. IRB Administrator maintains roster of IRB membership; prepares Dean's appointment letter and "welcome package' for new members; ensures availability of training materials and educational opportunities for IRB members; and creates accounting and disbursement infrastructure for compensation to Chairs and IRB members.

Applicable Regulations

21 CFR 56.107(a)
45 CFR 46.107(a)

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

Section 2.3
Orientation and Training

Policy

Training of Investigators, IRB members and IRB staff, and research personnel conducting research involving human subjects will meet the requirements set forth in the most recent version of the PHS *Policy on Instruction In The Responsible Conduct Of Research*. 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.

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, access to or copies of the following:

1. UCSD HRPP Standard SOPPs
2. UCSD IRB fact sheets on selected topics
3. FDA Information Sheets and Guidelines when issued
4. 45 CFR 46 (DHHS: Protection of Human Subjects)
5. The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects
6. 21 CFR 50 (FDA: Protection of Human Subjects)
7. 21 CFR 56 (FDA: Institutional Review Boards)
8. 21 CFR 812 (FDA: Investigational Device Exemptions)
9. 21 CFR 312 (Investigational New Drug Application)
10. OHRP Reports and Guidelines
11. Other materials as appropriate

All IRB members will complete the appropriate Collaborative Institutional Training Initiative (CITI) online training module(s) (at http://www.citiprogram.org) prior to starting as active members, and this will be documented. Prior to attending their first meeting as a voting member, a new IRB member should meet with the Chair or designee to discuss specific responsibilities and duties and familiarize him or herself with the IRB meeting format and sign the "UCSD Human Research Protections Program Confidentiality and Computer Security Agreement." Institutional Review Board 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, all IRB members and staff will be provided with a training session on the revised components, normally as part of a scheduled IRB meeting.

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).

The UCSD HRPP program website contains links to classroom training opportunities and also a links to online human research protections training maintained by CITI with input from 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 (https://irb.ucsd.edu) and also paper copies on request.

Ongoing Educational Programs

The HRPP 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. An on-line web tutorial for all investigators and IRB members that meets NIH training guidelines.
5. Educational programs for undergraduate students.
6. Educational sessions for Institute of the Americas graduate students
7. Educational sessions for UCSD medical students engaged in research as a component of their Independent Study Project (ISP).
8. Educational presentations to Pharmacy Fellows.

Procedures

1. IRB Administrator establishes new IRB member and staff orientation in the following:
    a) Regulations and Guidance: Drug (21 CFR 312) and Medical Device (21 CFR 812) FDA regulations; other FDA regulations (21 CFR 54); Protection of Human Subjects (21 CFR 50 and 56, 45 CFR 46); ICH guidelines; other guidelines (Belmont Report, Declaration of Helsinki, etc.); and applicable FDA and OHRP guidance documents.
    b) Policies, Procedures and Operations: review of forms (IRB, FDA); site reviews and reports; expedited reviews; reviewing adverse event reports; reviewing recruitment materials/advertisements; scheduling meetings; conducting reviews, including new and continuing reviews; support staff

responsibilities; access to written resources; and confidentiality requirements.

c) New staff training in the following: use of office computer systems; management of electronically submitted applications and reviews ("e-IRB"); paper files and archiving; interactions with Sponsors and Investigators; applications for New and Continuing Review; and Initial review of project-related correspondence.
d) Conduct and document education of new members and staff and periodic continuing education of existing members and staff and maintain access to relevant regulatory and clinical reference materials.

Applicable Regulations

21 CFR 56.107 (a)
45 CFR 46.107 (a)
Policy on Instruction In The Responsible Conduct Of Research

References, Forms, and Links

Training links of UCSD HRPP program website: https://irb.ucsd.edu

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

Section 3.1
Initial Screening

Policy

Applications will be screened by HRPP program staff. Those qualifying for "expedited review" as established by the Secretary, DHHS, (see Expedited Review) will be sent to the appropriate IRB Chair or designee(s) for review. Those qualifying for "exemption from IRB review" as established by the Secretary, DHHS, (see Exemption from IRB Review) will be sent to the appropriate IRB Chair or HRPP Director 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." The determination as to whether an activity represents human subjects research will be made by the IRB Chair or the Chair's designee. The criteria to make the determination include the following:

1. The activity involves human participants
2. The activity is a systematic investigation including research development, testing and evaluation.
3. The activity is designed to develop or contribute to generalizable knowledge.

If a project is determined to not meet the criteria, the individual will be informed of this determination either via telephone, e-mail or written document.

Applications that meet DHHS, FDA, or UCSD HRPP definitions of "human subjects" and "research" must be approved by an IRB unless the research has been determined to be exempt from IRB review.

Applications that meet the definition of "research involving human subjects" according to DHHS and FDA 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 convened IRB review. 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 "re-assigned" to another IRB or to a subsequent meeting of that IRB where such expertise is present. These evaluations, assignments and determinations are initially done by an HRPP analyst with review and approval by the IRB Chair, the HRPP Director, or an HRPP Associate Director. If the protocol to be reviewed involves a commercially sponsored drug, device or biologic study, at minimum, copies of the sponsor's master

protocol, investigator's brochure and the UCSD protocol and consent document(s) will be available to the IRB for review.

Procedures

1. Initial submissions will be screened to determine whether the study qualifies as human subjects research or a clinical investigation based on the DHHS, FDA, or UCSD HRPP definition of "research involving human subjects" and if necessary will use the worksheet "Determining Whether a Proposed Activity is Human Research."
2. If the activity is not "human subjects research" as defined by DHHS, FDA, or UCSD HRPP definitions, 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.
3. Prior to full IRB review, initial submission applications will be screened by HRPP staff using a checklist, "Initial Submission Screening Checklist," to determine whether appropriate documents has been provided and whether criteria for expedited review or exempt from IRB review are satisfied. For applications not providing appropriate documents, 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. Those meeting expedited criteria, will be assigned to the appropriate HRPP analyst for expedited review. Those applications that appear to meet exempt criteria will be assigned to an IRB Chair or the HRPP Director.
4. For applications that meet the definition of "research involving human subjects" and require convened Committee review, a primary and a secondary reviewer will be assigned from the members of the IRB based on reviewer expertise (and any other relevant consideration, such as individual background and experience). 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 "re-assigned" to another IRB or to a subsequent meeting of that IRB where such expertise is present. These evaluations, assignments and determinations are initially done by an HRPP analyst with review and approval by the IRB Chair, the HRPP Director, or an HRPP Associate Director.
5. HRPP designated staff will ensure documents associated with the IRB meeting are available and ready for review.

Applicable Regulations

45 CFR 46.101
45 CFR 46.108
45 CFR 46.109
45 CFR 46.110
45 CFR 46.116(d)

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

Section 3.2
Convened IRB Review

Policy

During initial review, the IRB reviews new proposals for research involving human subjects submitted by investigators. The purpose of initial review is to ensure protection of the safety, rights and welfare of research participants and compliance with Federal laws and institutional regulations for the protection of human subjects. The IRB has the authority to disapprove, defer, 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 IRB requests substantive clarifications or modifications that were directly relevant to the determinations required by the IRB, the protocol cannot be approved without a review of the responsive information by a convened IRB.

IRB members and consultants must self-disclose potential conflict of interest prior to reviewing protocols for which there may be conflict of interest. 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 the IRB.

Initial Review Process

These guidelines should be followed in the conduct of the initial review of all applications reviewed at a convened IRB meeting.

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 are made available to the all IRB members for review: application Facesheets; completed Research Plan; informed consent/assent documents; master protocol; grant submission materials, and/or investigator brochure, investigational drug fact sheet; and/or package insert(s), (if applicable); recruitment materials; and support letters (if applicable).

Review of the Initial Application

The application will be reviewed by the convened 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 primary and secondary reviewers, as well as the other IRB members, and voted upon. The reviewers will use a worksheet such as the Reviewer's Checklist to ensure that each of the specific criteria for approval were reviewed and have been met. Worksheets will then be associated with the appropriate study file electronically.

Review of the Investigator and Investigative Site

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

Review of the Informed Consent Form

The informed consent form will be reviewed by the secondary reviewer and the convened 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 convened IRB prior to approval or can be reviewed by the Chair and/or designee via expedited review. The reviewers will use a worksheet such as the Reviewer's Checklist to ensure that each of the specific criteria for approval were reviewed and have been met.. Worksheets will then be associated with the appropriate study file electronically.

Approval of Research

When the approval of research is contingent on specific minor conditions that can be approved by an IRB Chair, IRB member, or Chair designee, the IRB will be informed and advised of such expedited actions using the "Summary of actions since last meeting" link provided on the meeting agenda page. Documentation that the IRB was provided with this information will be included in the meeting minutes.

Protection of Vulnerable Populations

If the research study proposes to recruit subjects from vulnerable populations, the IRB will review, discuss, and/or require modification for minimizing undue influence on vulnerable subjects in accordance with applicable federal regulations.

Protection of Confidentiality

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

Conflict of Interest Disclosure

The IRB will review the conflict of interest portion of the application. The IRB 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 has independent review committees for conflict of interest, and that the findings of these committees, because they may occur after initial IRB approval of a project, may lead to subsequent modifications of Research plan and consent or other actions.

Payment to Subjects

The IRB will determine whether proposed payments to subjects are appropriate and do not represent an undue influence on the trial subjects. Payments to a subject should be prorated and not wholly contingent on completion of the trial by the subject.

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. The method, amount, and schedule of payment should be stated in the consent form

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.

Review of Advertisements and Recruitment Methods

IRB 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:

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 approved advertisements or ad text will be reviewed and stamped by the IRB.

Safety Monitoring

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

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.

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:

1. 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;
2. 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;
3. 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;

4. 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
5. The investigation is conducted in compliance with the requirements of 21 CFR 312.7.

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

In studies using pharmaceutical products (particularly when an investigational product is involved), a pharmacist from the UCSD Investigational Drug Service may be asked to review the Investigator's Brochure and communicate any concerns or suggested modifications to the IRB. When an IND is provided, the number will be checked 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.

Rapid-Cycle Review for Phase IIb, Phase III and Phase IV Industry-Sponsored Clinical Trials

Phase IIb studies provide researchers with additional safety data, confirm clinical efficacy of a drug and determine the therapeutic dose range. Researchers use these data to refine research questions and develop research methods. If preliminary evidence suggesting effectiveness of an investigational drug is found in a Phase II clinical trial, a Phase III clinical trial may be done.

Phase III trials typically compare the "new" treatment to a "standard" treatment or no treatment and the choice of treatment may be randomly assigned and the data blinded. Phase III trials may include hundreds to thousands of participants around the country and around the world and are intended to gather additional information to evaluate the overall risk/benefit relationship of the drug and provide an adequate basis for physician labeling. As noted by NIH, "While short-term risk is usually slight, one must consider the long-term effect of the study agent or achievement of significant safety or efficacy differences between control and study groups…." Though not required by the FDA, such trials typically have a Data Monitoring Committee (also known as a Data and Safety Monitoring Board (DSMB) or a Data and Safety Monitoring Committee (DSMC)) and the FDA recommends sponsors consider using a Data Monitoring Committee when the study is large, of long duration, and multi-center.

A Phase IV clinical trial is a post-marketing study of a drug that is approved by the FDA and has more participants than Phase III clinical trials. Phase IV trials are done to obtain additional information regarding the drug's efficacy, toxicity, and long-term effects.

The UCSD IRBs have determined that in light of this information regarding Phase IIb, Phase III and Phase IV clinical trials, a rapid-cycle review may be used to evaluate such trials if the trial meets the following criteria:

1. The project is a "clinical trial" according to the FDA definition of a clinical trial.
2. The project is a Phase IIb or Phase III or Phase IV clinical drug trial.
3. The project is industry-sponsored but not PI-initiated.
4. The project is being conducted under a clinical trial agreement directly between an industry sponsor and UCSD (that is, it does not require a contract with another entity, such as a non-profit, academic institution, or federal or state funding agency) where the agreement is being negotiated through OCTA.
5. The application is considered complete. That is, the application includes all documents necessary for an appropriate review by the convened IRB including signed Application Facesheets, Master Protocol, Investigator Brochure, Research Plan, consent document and other study documents, as needed.
6. Confirmation that the project has a DSBB or DSMC in place.

IRB Procedures

The following procedures are designed to enable a rapid-cycle review of Phase III or Phase IV industry-sponsored clinical trials such that the IRB review and all correspondence with the PI necessary for approval may be completed within three weeks of complete application submission to the IRB.

1. HRPP staff will screen the application for eligibility for rapid-cycle review. Screening involves the use of a checklist to ensure that the rapid-cycle review criteria are satisfied:
2. Once determined to meet eligibility, the project will be placed on an IRB meeting agenda and assigned to a primary IRB reviewer, who is an IRB member with appropriate scientific expertise, and a secondary reviewer, who is also an IRB member.
    a) The primary reviewer will primarily focus his or her review on the Research Plan including the following:
        1. Scientific merit.
        2. Informed consent and recruitment processes.
        3. Risks and risk management.
        4. Risk/benefit ratio.
        5. Conflict of interest.
    b) The secondary reviewer will primarily focus his or her review on the informed consent document(s) "local context" including the following:
        1. Accuracy of local contact information.
        2. Consistency of harm clause language with UCSD policy.
        3. Presence of a Moore clause, if applicable.
        4. Appropriate wording/content used in a UCSD consent.
3. The outcome of the IRB review should be communicated in writing to the PI within 3 business days of the IRB meeting at which the project was reviewed.
4. Upon approval of the project, the PI, OCTA, and OCAA will be notified by email that the project has been approved by the IRB, and informed consent documents will be released once the clinical trial agreement has been finalized

and an appropriate determination from OCAA has been received by the HRPP Office.

Approval and Documentation

The IRB will vote according to the categories of action described in SOPP, Section 4.2, Categories of Action. 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 for approval of a research study have been met. The results of IRB review and actions taken by the IRB should be communicated to the investigator and institutional officials, as appropriate, in writing and within 3 business days. Documentation will include the basis for requiring revision to the application or reason for approved pending, deferring, or disapproving of the research.

Initial Review of Investigational Devices

The United States Food and Drug Administration (FDA) provides the regulations regarding review of research associated with devices. These regulations include 21 CFR 50 ("Protection of Human Subjects"); 21 CFR 56 ("Institutional Review Boards"), and 21 CFR 812 ("Investigational Device Exemptions").

Guidance from the FDA notes that a medical device is an instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including any component, part, or accessory, which is recognized in the official National Formulary or the United States Pharmacopeia, or any supplement to them; intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man or other animals; or intended to affect the structure or any function of the body of man or other animals, and which does not achieve its primary intended purposes through chemical action within or on the body of man or other animals and which is not dependent upon being metabolized for the achievement of its primary intended purposes. [21 U.S.C. 321(h)]

When the proposed research involves an investigational device, the IRB will determine whether the device 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 including a description of the device, and reports of prior investigations conducted with the device, a copy of the FDA's device determination letter, and other sources as applicable. The investigator and/or sponsor should also provide a clear and specific risk assessment as well as their rationale in making the SR or NSR determination.

The determination of device risk will be based on the proposed use of the device, as well as any protocol-related procedures and tests, and not the device alone.

If the device has previously been determined to be a SR or NSR device by the FDA, it will be treated as such by the IRB. Guidance form the FDA notes that the agency's determination is final. When an IDE is provided, the IRB will confirm that number is on

file with the FDA. 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.

If the device has previously been determined to be a NSR device by the sponsor, 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 documented in the minutes.

The SR/NSR determination will be conducted before the IRB conducts the review of the study under 21 CFR 56 and 45 CFR 46. Guidance from the FDA includes "The judgment about whether a study poses a significant risk or nonsignificant risk is based on the significance of the potential harm that may result from participation in the study including the use of the device; whereas the IRB's decision to approve for implementation is based on the study's risk-benefit assessment."

Significant Risk Devices

A device will be determined to be a significant risk device if any of the following criteria apply:

1. The device is intended as an implant.
2. The device supports or sustains human life.
3. The use of the device is of substantial importance in diagnosing, curing, mitigating, or treating disease, or preventing impairment of health.
4. The device could cause significant harm to any subjects.
5. The subject must undergo a procedure as part of the device study.
6. The device appears on the FDA list of significant risk devices.
7. The study or any of the study procedures could cause harm to the subjects which:
    a) Could be life threatening,
    b) Could cause permanent impairment of a body function,
    c) Could cause permanent damage to body structure, or
    d) Could necessitate medical or surgical intervention to preclude permanent impairment of a body function or preclude permanent damage to body structure.

When the IRB determines that the device is a significant risk device, and an IDE is not provided with the submission, the IRB 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.

Non-significant Risk Devices

A non-significant risk device is a device that does not meet the definition of a significant risk device.

If the investigator and/or sponsor identifies a study as NSR, the investigator must provide an explanation of such determination and any other information that may help the IRB to evaluate the risk of the study/device including a clear description of the device, reports of prior investigations with the device other information as appropriate.

When the IRB determines that the device is a non-significant risk device, the IRB 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. The FDA considers an NSR device study to have an approved IDE after IRB approval and when sponsors meet the abbreviated requirements at 21 CFR 812.2(b). If those abbreviated requirements are met, the sponsor is considered to have an approved IDE in place.

Exempted Devices

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

1. 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.
2. 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.
3. 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 the investigation meets the IDE exemption criteria at 21 CFR 812.2(c) (3); and there is NO possibility of linkage between the "leftover" sample, that is, remnants of specimens collected for routine clinical care or analysis that would have been discarded, and subject identification (e.g., surplus blood sample that is coded but the coding cannot be linked to the source subject) and where results of the investigational test are not communicated to or otherwise associated with the identified subject; individuals caring for the patients are different from and do not share information about the patient with those conducting the investigation including the sponsor; the specimens are provided to the investigator(s) without identifiers and the supplier of the specimens has established policies and procedures to prevent the release of personal information does not require Informed Consent compliance.

4. 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.
5. A device intended solely for veterinary use.
6. A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c).
7. A custom device as defined in Sec. 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

510(k) Device

The FDA notes that a premarket notification, or 501(k), is submitted to the FDA before a manufacturer proposes to market a medical device. If the FDA agrees the new device is substantially equivalent to a legally marketed device for which premarket approval is not required, the manufacturer may market the device immediately. The FDA does not require clinical data on most 510(k)s. The exemption in 21 CFR 812.2(c)(2) applies only to investigations in which the 510(k) product is being used in accordance with the labeling clearly by the FDA. However, if clinical data are necessary to demonstrate substantial equivalence, the clinical study must comply with the IDE, IRB and human subjects protection regulations. Further, "off-label" use of a 510(k) product take the product outside the exemption. A device subject to 510(k) remains investigational until the 510(k) is cleared by the FDA and the investigational use is subject to the requirements of the IDE, IRB and human subjects protection regulations [21 CFR 812, 50, and 56].

What is submitted to the IRB for review of an Investigational Device?

1. An appropriately completed Biomed Standard Facesheets and Biomedical Application Research Plan including such information as a clear and specific description of the device; a clear and specific risk assessment as to whether the device is SR or NSR, and the rationale used to make this determination; etc.
2. A copy of relevant reports of prior investigations conducted with the device.
3. A copy of the FDA's device determination letter.
4. Other sources of information regarding the device and use of the device, as appropriate.
5. The consent document(s) to be used.

Humanitarian Use Devices

A Humanitarian Use Device (HUD) is a device that is determined to meet specific requirements including scientific rationale and population prevalence by the Office of Orphan Products Development. As such, the general criteria for an HUD, as outlined on the FDA Website are as follows:

1. Expected to benefit fewer than 4,000 people in the US per year (in some FDA information sheets, worded more narrowly as "is designed to treat or diagnose a disease or condition that affects fewer than 4,000 individuals in the United States.").

2. No comparable device already available.
3. No exposure to "unreasonable or significant risk of illness or injury."
4. Potential benefits of the device outweigh its risks.

The FDA grants a Humanitarian Device Exemption (HDE) that authorizes the "marketing" of an HUD. A HDE is an application that is similar to a premarket approval (PMA) application, but is exempt from the effectiveness requirements of sections 514 and 515 of the Food, Drug and Cosmetic Act (the Act). FDA approval of an HDE authorizes an applicant to market a HUD, subject to certain profit and use restrictions set forth in section 520(m) of the Act.

Current draft guidance from the FDA notes that because an SR/NSR determination applies only to device research studies, when the HUD is being used within the approved labeling (i.e., not for research), the IRB is not required to provide a SR/NSR determination.

What is submitted to the IRB for review of a HUD?

Though the IRB recognizes that the use of an HUD is not typically research, for the initial review of the HUD, the IRB requests the following materials be provided:

1. An appropriately completed Biomed Standard Facesheets and Biomedical Application Research Plan providing such information as a summary of how the physician proposes to use the device; a description of any screening procedures; the HUD procedure; any patient follow-up visits, tests or procedures risks; how risks will be managed; justification that risks are reasonable in relation to the proposed use of the device; costs to the patient; privileges/certifications and licenses; etc.
2. A copy of the HDE approval order.
3. A clear and specific description of the device.
4. The product labeling.
5. The patient information packet.
6. The consent document to be used.

How is a HDE different from a Investigational Device Exemption (IDE)?

A HUD will most likely never obtain the efficacy data required for an ordinary Pre-Market Approval by the FDA. Although the HUD designation contains some of the elements found in an IDE, the "approval" for the use of a HUD includes the provisions that the IRB provide oversight (initial and continuing review). Guidance from the FDA notes "…once the HDE is approved, the HDE holder is responsible for ensuring that the approved HUD is only administered at institutions that have an IRB constituted and acting pursuant to 21 CFR 56 including conducting continuing review of the use of the HUD…HUDs should not be used until AFTER the HDE applicant obtains approval of the HDE from FDA and IRB approves its use. IRBs should ensure that HDE approval has been granted before approving the device for use at their institution." In addition, the clinician/investigator must abide by the label indications.

Clinicians and investigators must obtain IRB approval as stipulated in 21 CFR 814.124(a). It is suggested that the application contain a predefined number of recipients so that case-by-case IRB oversight is not required unless the IRB for some special reason decides that interims are necessary. The regulations also require that a fully convened IRB review the application. Although the device might be minimal risk in nature, the regulations do not allow expedited review. For continuing review, however, IRBs may use the expedited review procedures unless the IRB determines that convened board review should be performed.

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. When reviewing an HDE, the IRB will follow the review criteria in 21 CFR 56.111 and elsewhere in Part 56, and 45 CFR 46, as much as possible. The IRB will review the risks to patient and ensure that risk are minimized and that risks are reasonable in relation to the proposed use of the device.

Should an investigator or HDE holder develop a research protocol designed to collect safety and effectiveness data to support a PMA for the device, an IDE would not be needed if the research is within the approved labeling. However, IRB approval must be obtained before research may begin as this would be considered an FDA-regulated clinical investigation. Subjects must also be consented using an IRB-approved consent document. If the research is for a "new use," the IDE regulations must be followed. [21 CFR Parts 812, 50, and 56]

HUD and Informed Consent

The regulations, as provided by the FDA, state that informed consent is not required for the use of a HUD "Because an HDE provides for marketing approval, use of the HUD does not constitute research or an investigation which would normally require consent from the study subjects." Guidance from the FDA includes, "However, there is nothing in the law or regulations that prohibits a state or institution from requiring prospective informed consent, when feasible."

UCSD IRBs **require** review and approval of a consent document when a study is associated with an HUD/HDE. It is suggested that the clinicians/investigator, for purposes of documentation, should note that the patient has been told that the device has not been licensed in the ordinary manner (and/or that it has not been proven to be safe and effective by the usual criteria). Participants should also be provided with current labeling information if available. Typically, the consent will include information provided in the patient information packet such as a description of any ancillary procedures associated with the use of the HUD; a description of the use of the HUD; all know risks or discomforts; an explanation of how the device may work in relation to the disease or condition, etc., as well as stating, "A Humanitarian Device Exemption is a special FDA category for a device that can be used by a physician that is exempt from FDA effectiveness requirements and for which no comparable is available to treat [the disease or condition]. The device is intended to benefit patients in

the [treatment or diagnosis] of your condition in 4,000 individuals in the United States per year. The effectiveness of this device for this use has not been demonstrated."

Off-label Use of a HUD

The FDA requires that the off-label use of a HUD be reported to the IRB and that the investigator notifies the manufacturer of the proposed use of the device. As such, the use might constitute an amendment to the HDE or may require an IDE.

The off-label use of a HUD in an emergency that cannot wait for IRB action should be treated in the same manner that an emergency use of an investigational drug or device of any other type would be handled. Criterion for the emergency off-label use would include the following:

1. A life-and-limb-threatening emergency and that the urgency of situation does not allow time for IRB review
2. No other standard (or already IRB-approved) intervention available can be used with a reasonable chance of success
3. No regulatory barriers (i.e., within HDE provisions, or steps begun to obtain special approval) (usually handled by emergency communication with HDE sponsor)
4. (If consent must be waived) Physician uninvolved in patient's care concurs

A formal report to IRB within 5 working days including identification of the patient involved, the date of use, and the reason for the use; formal application must be provided if additional patients likely.

Review 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 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 and/or reason for disapproval of the research.

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/permission/assent documents or request for waiver of consent/permission/assent, 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.

Applicable Regulations

21 CFR 50
21 CFR 54
21 CFR 312
21 CFR 812.2(b)(1)(ii)
21 CFR 812.66
21 CFR 814.124(a)
21 CFR 56.107(e-f)
21 CFR 56.108(a)(1-2)
21 CFR 56.108(c)
21 CFR 56.109(a-f)
45 CFR 46.103 (b) (4-5)
45 CFR 46.107 (e, f)
45 CFR 46.108 (a)
45 CFR 46.108 (b)
45 CFR 46.109 (a-e)
45 CFR 46.110(c)
45 CFR 46.111
ICH 3.1
Federal Food, Drug and Cosmetic Act
California Health and Safety Code 445

Links

http://www.hhs.gov/ohrp/policy/index.html - OHRP Policy Guidance website
http://www.fda.gov/oc/gcp/regulations.html - FDA Regulations
http://www.fda.gov/oc/gcp/default.htm - FDA Good Clinical Practice website
http://www.ncbi.nlm.nih.gov/PubMed/ - PubMed MEDLINE
http://www.rxlist.com/script/main/hp.asp - Drug information from Rxlist.com
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm110203.pdf - Guidance for Humanitarian Device Exemption
http://www.fda.gov/oc/ohrt/irbs/devices.html - Guidance for IRBs and Clinical Investigators regarding Medical Devices
http://www.fda.gov/oc/ohrt/irbs/devrisk.pdf - Guidance for IRBs, Clinical Investigators and Sponsors regarding Significant Risk and Nonsignificant Risk Medical Device Studies
http://www.fda.gov/oc/ohrt/irbs/irbreview.pdf - Guidance for IRBs, Clinical Investigators and Sponsors FAQ about Medical Devices
http://www.fda.gov/downloads/MedicalDevices/DeviceRegulationandGuidance/GuidanceDocuments/ucm080203.pdf - Guidance on IDE Policies and Procedures.

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

Section 3.3
Criteria for Approval

Policy

In order to be approved, a project must meet the criteria for approval in this section. This is true of projects reviewed through a convened 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. The IRB approval occurs when the HRPP releases an approval letter containing the approval date.

Required Criteria

The following requirements must be satisfied in order for the IRB to approve proposed research:

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. Additional information to consider includes whether there is/are resources necessary to protect subjects; adequate time for the investigators to conduct and complete the research; adequate number of qualified staff; adequate facilities in which to conduct the research; access to population that will allow recruitment of the necessary number of subjects; and medical or psychosocial resources available that subjects may need as a consequence of the research.
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.

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. 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.

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 their information when applicable. Some examples of the types of questions the IRB should ask about the research when determining the adequacy of managing participant's privacy concerns include the following:
    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., placebo, 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. If the sponsor or IRB requires a witness to the consenting process in addition to the witness to the participant's signature and if the same person needed to serve both capacities, a note to that effect must be placed under the witness's signature line.
8. 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 may be periodically reviewed for select studies by the IRB or designated reviewers, such as UCSD auditors. Findings will be shared with the IRB Steering Committee or as delegated.

Procedures

1. Reviewer(s) will assess risks, benefits and the adequacy of subject protections; determine whether approval criteria have been met; and make recommendations as to IRB action.
2. IRB members will discuss project in light of approval criteria and vote on approval.
3. IRB Administrator will document in the minutes that approval criteria have been met if approval has been granted and maintain reviewer written comments.

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
ICH 3.1

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

Section 3.4
Informed Consent

Policy

No investigator may involve a human being as a subject unless legally effective informed consent has been obtained from the subject or the subject's legally 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.

In order to assess the informed consent process, the submission to the IRB should be detailed enough to allow the IRB to determine that an appropriate process will be followed. 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 also review and 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.

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 legally 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, and Rady Children's Hospital – San Diego. However, all consent forms must contain the elements required by federal regulations. 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 Experimental Subject's 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.

The written consent form may be either of the following:

1. A written consent document that embodies the elements of informed consent described in 21 CFR 50.25 and 45 CFR 46.116. This form may be read to the subject or the subject's legally 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.
2. 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 legally authorized representative. When this method is used, there will be an impartial witness to the oral presentation, and the following four documents are required:
    a) A copy of the IRB-approved English short form translated into the language in which the subject is fluent. The UCSD IRB-approved English short form has been translated into the following languages: Spanish (form and certificate), Vietnamese (form and certificate); Chinese, Simple (form and certificate) and Traditional (form and certificate); Arabic (form and certificate); and Somali (form and certificate).
    b) A copy of the IRB-approved study consent (long form).
    c) A copy of the UCSD "Experimental Subject's Bill of Rights" translated into the language in which the subject is fluent. The UCSD "Experimental Subject's Bill

of Rights" has been translated into the following languages: Spanish (form and certificate); Vietnamese (form and certificate); Chinese, Simple (form and certificate) and Traditional (form and certificate); Arabic (form and certificate); and Somali (form and certificate).

d) If the procedures for using the short form were not previously approved, a revised Research Plan to clearly and specifically outline the procedures that will be used to obtain consent using this method.

These procedures should also address the ongoing process of "informed" consent and the need for providing continued, qualified interpretive services. These four documents require IRB approval before using the short form to obtain consent.

In addition, the following persons need to be present at the time short form consent is being obtained:

a) The potential participant.
b) The person obtaining consent.
c) A qualified interpreter. A family member or close personal friend of the participant is not considered a qualified interpreter. The qualified interpreter may be present physically or by some other means, for example by phone or video conference. Note that the interpreter may also serve as the witness only if the interpreter can sign the appropriate documents (see below).
d) A witness. The witness is an adult who is conversant in language of the presentation. The witness should be an impartial third party, not otherwise connected with the clinical investigation (for example, clinical staff not involved in the research or a patient advocate) and not be the person obtaining the consent. The purpose of the witness is generally to attest to the voluntariness of the subject's consent and the adequacy of the consent process by ensuring that the information was accurately conveyed and that the subject's questions were answered.

The following signatures are required if the potential participant agrees to enroll in the study:

a) The participant signs and dates the translated short form and the translated "Experimental Bill of Rights."
b) The person obtaining the consent signs and dates the IRB-approved study document.
c) The witness signs and dates the translated short form and the IRB-approved study consent.

Copies of all the documents are provided to the participant.

Once the participant has been consented, the English version of the IRB-approved study consent must be translated into the language in which the participant is fluent. The translated document must be submitted for approval by the IRB (typically using expedited procedures), and provided to the participant as soon as possible but no more than one month after the participant's initial consent.

The short form method should be used only for the occasional and unexpected enrollment of non-English speaking participants.

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.

A witness signature is needed only if required by the IRB including when the short form consent method is used or consent is obtained from a subject who does not read or speak English or is illiterate. Note that the witness, except when using the short form, is required to witness only the subject's or subject's legally authorized signature, not the informed consent process, unless the sponsor or the IRB requires the witness to witness the informed consent process. The witness cannot be the person who obtained consent from the subject but may be another member of the study team or a family member unless the short form consent procedures are used.

A signature line for the subject's legally 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 SOPP Section 3.3.6, "Surrogate Consent and Review of Projects Involving Populations with Impaired Decisional Capacity" regarding research involving persons with impaired decisional capacity for additional information on this topic.

The research subject or legally authorized representative will be given a signed copy of the consent form, and a copy of the "Experimental Subject's Bill of Rights."

Use of Electronic Signatures for consenting subjects

Unless the IRB waives the requirement for signed consent, such as through 45 CFR 46.117(c), a written consent must be given to and signed and dated by the subject or the subject's legally authorized representative. An electronic signature on a consent document may be used if the procedures for obtaining electronic signature are approved by the IRB.

In order for the IRB to approve use of electronic signature on a consent form , the IRB will consider such issues as how the electronic signature is created, if the signature can be shown to be legitimate, and if the consent document can be produced in hard copy for review by the potential subject. As noted by OHRP, "If properly obtained, an electronic signature can be considered 'original' for the purposes of recordkeeping."

The Office of Human Research Protections also notes, "OHRP would allow electronic signature of the document if such signatures are legally valid within the jurisdiction where the research is conducted." Two laws that address the electronic signature of the consent include the Federal Electronic Signatures in Global and National Commerce Act (eSIGN) and California's Uniform Electronic Transactions Act (UETA). These laws include that the subject must agree to use the

electronic format, such as by clicking a "You agree" icon, and a clear statement of the subject's rights with respect to the electronic document is provided. The rights include the right to obtain the electronic record in non-electronic form and a description of any procedures that must be followed to withdraw the subject's agreement to use an electronic record.

In addition, for FDA-regulated research, "electronic" documents would be subject to a specialized set of requirements found at 21 CFR Part 11. Compliance with these standards is used to assure that electronic records are "trustworthy, reliable, and generally the equivalent to paper records and handwritten signatures executed on paper."

Required Elements of Informed Consent Forms

In accordance with 21 CFR 50.25 and 45 CFR 46.116, 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. For sponsored studies, a statement naming the organization that will pay for injury costs should be included.
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. If the research involves products regulated by the FDA or will be used to support applications for products regulated by the FDA (a drug with an IND or a medical device with an IDE), the consent form will include a statement disclosing that the FDA may choose to inspect research records identifying study participants.
10. When seeking informed consent for clinical trials approved after March 7, 2012 that require registration in the clinical trial registry databank, the following wording must be included in the consent, "A description of this clinical trial will be available on http://www.ClinicalTrials.gov, as required by U.S. Law. This Web site will not include information that can identify you. At most, the Web site will include a summary of the results. You can search this Web site at any time."

11. 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 eighth-grade reading level or lower.

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. This information should include whether the investigator believes the specimens obtained could be part of or lead to the development of, a commercially valuable product. If so, a Moore clause should be included in the consent.
8. Future use of collected specimens should specimens be retained at the end of the study including where the specimens will be retained, who will have access to them, how long they will be retained, what information will be associated with the specimens, and what information will be provided with the specimens should they be shared with other individuals outside the current project.
9. Whether subjects will be recontacted for future research.
10. Whether subjects will receive a report of the aggregate results or any results specific to the subject and the procedures associated with providing the results.
11. 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.
12. A description of any financial or other arrangements with a sponsor or institution that may pose a conflict of interest.
13. Any additional information that may be required by state, federal, or institutional regulations in order for informed consent to be legally effective.
14. 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.

Waiver or Alteration of Informed Consent.

For FDA-regulated research, waivers of consent are 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 IRB may waive the requirements to obtain informed consent if the IRB finds that all of the following conditions apply:

1. The research is minimal risk.
2. The waiver will not adversely affect the rights and welfare of the subjects.
3. The research could not practicably be carried out without the waiver.
4. Whenever appropriate, the subjects will be provided with additional pertinent information after participation.

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 individual authorization for research uses of PHI 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.

Obtaining Consent from Individuals Who Cannot Read or Speak English or Who are Illiterate

As noted by the FDA, "The investigators and the IRBs that review such research should carefully consider the ethical ramifications of enrolling or excluding potential subjects when a language barrier may exist between the investigator(s) and some or all of the potential subjects. Consistent with the requirement that selection of subjects be equitable (21 CFR 56.111(a)(3)), individuals should not routinely be excluded from participating in research simply because they do not understand English."

If it is likely that the study will enroll individuals who cannot read or speak English, the Research Plan must describe the procedures that will be used to obtain consent from these subjects including the use of documents translated into the subject's primary language, the use of a qualified translator, and how it will be ensured that continued, qualified interpretive services to the participant will be provided.

The subject must be given an IRB-approved translation of the consent form and the Experimental Subject's Bill of Rights in a language in which the subject is fluent. Unless the researchers are fluent in the subject's language, a qualified interpreter must be included in the consent process, either physically or by some other means, for example by phone or video conference, during the entire consent process, not just the signing of the consent form. A relative who speaks English does not qualify as an official interpreter.

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. An impartial witness will observe 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 in the Research Plan the procedures associated with obtaining consent from these subjects.

Procedures for obtaining informed consent from potential subjects who are physically unable to talk or write

If an investigator wishes to include a subject who can understand and comprehend spoken English but is physically unable to talk or write, the prospective subject must be competent and able to indicate approval or disapproval by some means. The consent will be read to the subject in the presence of an impartial third party who will witness the entire consent process, read the informed consent and any other written information provided to the subject, and sign the consent document beneath the subject signature line. An impartial third party is an individual who is independent of the trial and who cannot be unfairly influenced by people involved in the trial. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the subject, and consent was freely given by the subject. The consent should document the specific means by which the prospective subject communicated agreement to participate in the study as well as why consent was obtained in this manner and who the impartial third party was. If it is likely that the study will enroll individuals who physically are unable to talk or write, the Research Plan must describe the procedures that will be used to obtain consent from these subjects.

Procedures

1. IRB members will review informed consent forms for compliance with applicable federal, state and institutional regulations and policies; assess reading level and general readability of the form; and make recommendations on the adequacy of the form for its intended purpose and require changes if necessary.

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
45 CFR 46.117
FDA Guide to Informed Consent – Information Sheet
Electronic Signatures in Global and National Commerce Act
Uniform Electronic Transactions Act
California Health and Safety Code Section 24170-24179.5

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

Section 3.5
Emergency Use and Informed Consent

Policy

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 to be conducted in VA facilities. VASDHS investigators will comply with relevant VA policy on research in emergency settings.

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 5 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.

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.

Procedures

1. The IRB Chair will review Emergency Use documentation provided by the investigator in a timely manner and decide whether an emergency conference call of the IRB is indicated to discuss the matter.
2. The IRB Administrator will maintain telephone contact with investigator to quickly secure necessary documentation; schedule emergency use review meeting by conference call or in person in a timely manner; and provide investigator with relevant correspondence in a timely manner.

Applicable Regulations

21 CFR 50.20
21 CFR 50.23(a-d)
21 CFR 50.24
21 CFR 56.104(c)
45 CFR 45.116
VHA Handbook 1200.05

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

Section 3.6
Privacy and Confidentiality of Research Records

Policy

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

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

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

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 Individual Authorization for Research Use of PHI, appropriate UCSD authorities must receive from the researcher requesting the disclosure of PHI, the 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

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 individuals' 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.

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
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.

Procedures

1. IRB members will review recruitment and data management plans for research projects for compliance with confidentiality protections.
2. Principal Investigators will obtain a Certificate of Confidentiality, as appropriate.

Applicable Regulations

Privacy Rule of the Health Insurance Portability and Accountability Act of 1996, section 164.514
http://aspe.hhs.gov/admnsimp/bannerps.htm
http://privacyruleandresearch.nih.gov/pdf/clin_research.pdf
http://privacyruleandresearch.nih.gov/irbandprivacyrule.asp

Links

Website for Certification Information: http://grants1.nih.gov/grants/policy/coc/index.htm

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

Section 3.7
Protected Populations

Policy

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

In making such determinations the IRB will consider the nature and degree of risk, the condition of the particular population involved, and the nature and level of the anticipated benefits (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.

3.7.1 Projects Involving Prisoners

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.;

In addition to meeting Federal regulations, the project must comply with all state and local requirements for inclusion of prisoners as subjects. The IRB strongly encourages the Principal Investigator to contact HHS 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.

Procedures

1. The IRB Chair and IRB members will review the benefits of participation to ensure there are no coercive elements; ensure that the protocol and consent provide adequate protections for vulnerable populations; and verify that the research is in compliance with federal and institutional directives regarding vulnerable populations.
2. The IRB Administrator will review the application to ascertain if vulnerable populations are likely to be recruited; secure a voting member who is a prisoner/prisoner advocate; and secure additional consultations to provide additional expertise on special populations.

Applicable Regulations

45 CFR 46 Subpart C
OHRP Guidance on the Involvement of Prisoners
OHRP Prisoner Frequently Asked Questions
California Penal Code, Sections 3500-3524

3.7.2 Projects Involving Students and Employees

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 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.

Procedures

1. The IRB Chair and IRB members will review the benefits of participation to ensure there are no coercive elements; ensure that the protocol and consent provide adequate protections for vulnerable populations; and verify that the research is in compliance with federal and institutional directives regarding vulnerable populations.
2. The IRB Administrator will review the application to ascertain if vulnerable populations are likely to be recruited and secure additional consultations to provide additional expertise on special populations.

3.7.3 Projects Involving Pregnant Women

Pregnant women and fetuses are considered protected populations, and research must provide the additional protections listed here.

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.

Procedures

1. The IRB Chair and IRB members will review the benefits of participation to ensure there are no coercive elements; ensure that the protocol and consent provide adequate protections for vulnerable populations; and verify that the research is in compliance with federal and institutional directives regarding vulnerable populations.
2. The IRB Administrator will review the application to ascertain if vulnerable populations are likely to be recruited and secure additional consultations to provide additional expertise on special populations.

Applicable Regulations

45 CFR 46 Subpart B
The NIH Revitalization Act of 1993 (Public Law 103-43)
Section 498B of the Public Health Service Act (42 U.S.C. 298g-2)

3.7.4 Projects Involving Fetuses or Fetal Tissue

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.

Research conducted by UCSD investigators that is funded by federal agencies 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.

Procedures

1. The IRB Chair and IRB members will review the benefits of participation to ensure there are no coercive elements; ensure that the protocol and consent provide adequate protections for vulnerable populations; and verify that the research is in compliance with federal and institutional directives regarding vulnerable populations and fetal tissue.
2. The IRB Administrator will review the application to ascertain if vulnerable populations are likely to be recruited and secure additional consultations to provide additional expertise on special populations.

Applicable Regulations

45 CFR 46 Subpart B
The NIH Revitalization Act of 1993 (Public Law 103-43)
OHRP Guidance Fetal Tissue Transplantation
Section 498B of the Public Health Service Act (42 U.S.C. 298g-2)

3.7.5 Projects Involving Children and Adolescents

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 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.

Definitions

For purposes of this policy the following definitions are used, consistent with federal (45 CFR 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 fro 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)

Procedures

1. The IRB Chair and IRB members will review the benefits of participation to ensure there are no coercive elements; ensure that the protocol and consent provide adequate protections for vulnerable populations; and verify that the research is in compliance with federal and institutional directives regarding vulnerable populations.
2. The IRB Administrator will review the application to ascertain if vulnerable populations are likely to be recruited and secure additional consultations to provide additional expertise on special populations.

Applicable Regulations

45 CFR 46 Subpart D
OHRP Special Protections for Children as Research Subjects
OHRP Research Involving Children Frequently Asked Questions

3.7.6 Projects Involving Surrogate Consent and Populations with Impaired Decisional Capacity

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.

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 UCSD IRB 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.

<u>Determination of decisional capacity</u>

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.

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

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

1. Whenever possible, investigators will attempt to obtain informed consent directly from the subject.
2. If the potential research subject is obtunded, unconscious or otherwise obviously lacking in decision-making capacity, the investigator shall:
    a) Document that observation in the research record and in the subject's medical record;
    b) Proceed with the steps listed below under *Identifying Persons to Provide Surrogate Consent*
3. If the potential research subject has questionable capacity to consent but is not unresponsive, the investigator shall:

a) Consistent with the standard consent process, describe the research to the subject;
b) Perform and document an assessment of the participant's decisional-capacity relevant to the information provided about the research study;
c) If lack of decisional capacity is evident, the investigator shall inform the potential research subject of the investigator's intent to obtain surrogate consent;
d) If the subject expresses resistance or dissent to participation or to the use of surrogate consent by word or gesture, the subject shall be excluded from the research study.
e) If no resistance or dissent is expressed by the potential research subject, the investigator shall document this fact, and document that the description of the research project was communicated to the subject by placing a note in the medical record and in the research record.
f) Proceed with the steps listed below under *Identifying and Informing Persons providing Surrogate Consent*

Identifying Persons to Provide Surrogate Consent

In a non-emergency room environment

Surrogate consent may be obtained from any of the following potential surrogates who has reasonable knowledge of the subject, in the following descending order of priority:

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

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

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

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.

In an emergency room setting

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

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

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

Obtaining Consent from the Surrogate

1. Investigators shall describe to potential surrogates the nature of ongoing decisions during the study regarding the subject's participation, decision to participate in certain procedures, changes to the study, etc., in order to ensure that the surrogate will be willing to undertake these on-going responsibilities.
2. The surrogate shall complete the "Self-Certification of Surrogate Decision Makers for Participation in Research" form as an attachment to the informed consent document for the research study, and be given a copy of this form along with a copy of the consent to keep. In addition, the researcher must keep the signed form in the research records along with the signed consent. The "Self-Certification of Surrogate Decision Makers for Participation in Research" form verifies the willingness of the person to serve as a surrogate, details the relationship of the surrogate to the subject and the surrogate's qualifications demonstrating "reasonable knowledge" of the research subject. (Note: Section 3 of the "Self-Certification of Surrogate Decision Makers for Participation in Research" form is required only for surrogate consent in non-emergency room environment settings).
3. Potential surrogates must be advised that if a higher-ranking surrogate is identified at any time, the investigator will defer to the higher-ranking surrogate's decision regarding the subject's participation in the research.
4. For non-emergency room environment research only, if the potential surrogate identifies a person of a higher degree of surrogacy, the investigator is responsible to contact such individuals to determine if they want to serve as surrogate.
5. Surrogates are prohibited from receiving any financial compensation for providing consent. This does not prohibit the surrogate from being reimbursed for

expenses the surrogate may incur related to the surrogate's participation in the research.

6. Assessment of the decision-making capacity *of the surrogate* should be implemented only when the investigator has reason to believe that the surrogate's decision-making capacity may be impaired.

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

Re-consenting of Research Subjects

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

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.

Procedures

1. The Investigator will select appropriate individuals and methods for capacity determinations.
2. The IRB Chair and IRB members will 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.
3. The IRB Administrator will document in the file that additional approval criteria in this section have been met.

Applicable Regulations

American Psychiatric Association, "Guidelines for Assessing the Decision-making Capacities of Potential Research Subjects with Cognitive Impairments," American Journal of Psychiatry 155 (1998): 1649–50.

California Health and Safety Code, Section 24175 and 24178

National Bioethics Advisory Commission. Research Involving Persons with Mental Disorders That May Affect Decision-making Capacity, December 1998.

VHA Handbook 1200.05

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

Section 3.8
Financial Disclosure and Conflict of Interest

Policy

Financial Disclosure and Conflict of Interest for IRB Members

No regular or alternate IRB member may participate in the initial, deferral or continuing review, amendment request review, review by expedited procedure, review of unanticipated problems involving risks to subjects or others, review of non-compliance with the regulations or requirements of the IRB or report review regarding any project in which the IRB 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.

An individual cannot serve as regular or alternate IRB member or carry out day-to-day operations of the IRB review process if the individual is responsible for University business function or research development. For example, the Vice Chancellor for Research, the Dean School of Medicine, the Associate Director of the Office of Grants and Contracts, and the Director of Office of Clinical Trials Administration who are responsible for raising funds or garnering support for research cannot serve as a regular or alternate IRB member.

A conflict of interest is defined as a situation in which outside financial interests may compromise, or have the appearance of compromising, an investigator's professional actions or judgments in the design, conduct, or reporting of their research results. 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 IRB prior to discussion of the relevant issue, or may choose to remove 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, or IRB Vice-Chair should the IRB Chair declare a conflict, in consultation with the IRB Administrator, and if appropriate, the UCSD Conflict of Interest office.

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) in accordance with the same disclosure criteria required by investigators. 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.

If it has been determined that an IRB member has a conflict of interest associated with a project, the IRB member is excluded from discussion regarding the project except to provide information requested by the IRB, excluded from voting on the project, and must not be present during the discussion and voting. The IRB member with the conflict of interest is not counted towards quorum on that project.

Financial Disclosure and Conflict of Interest for Investigators

The principal investigator and all co-investigators 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 or other appropriate form(s) as determined by the Conflict of Interest Office. The forms and additional information regarding conflict of interest and human subjects research are available online from the UCSD Conflict of Interest Office website (http://ocga.ucsd.edu/). This disclosure policy applies to the principal investigator, co-investigators, 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 or any arrangement where the amount of compensation will be affected by the outcome of the research. The IRB takes into consideration whether the potential conflicts of interests might adversely affect subject welfare. The UCSD Independent Review Committee (IRC) work with the investigator to take steps to manage reduce or eliminate the conflict.

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

Review of 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.

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.

Procedures

1. IRB members including Chair and alternates must report conflict of interest(s) and potential conflict of interest(s) during meeting discussions.
2. IRB Administrator or staff designee will review discussions of conflict of interest issues and oversee disclosure in consent documents. The minutes will document the IRB member with the perceived conflict of interest associated with the study, an indication of what the conflict is and that the member was absent for the discussion and vote on the project.

Applicable Regulations

21 CFR 54.1
21 CFR 54.2
21 CFR 54.3
21 CFR 54.4
21 CFR 54.5
21 CFR 54.6
42 CFR 50.601
42 CFR 50.602
42 CFR 50.603
42 CFR 50.604
42 CFR 50.605
42 CFR 50.606
42 CFR 50.607
UC San Diego Conflict of Interest Office

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

Section 3.9
Exemption from IRB Review

Policy

The "Common Rule" (45 CFR 46 subpart A) defines a set of research activities that may be exempt from its purview, unless otherwise required by Department or Agency heads. Exempt research has very little, if any, associated risk.

These research activities, as defined by 45 CFR 46.101(b), include six exempt categories:

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.

Policy at UCSD allows the IRB to disallow exemptions that are allowable under federal law. At this time, only exempt categories 1-4 are allowed at UCSD.

The IRB Chair and/or the IRB Chair's designee may determine whether a submitted research project meets the requirements for exemption from IRB review. If the research project does not meet criteria for exemption, the PI will be notified and the project will require resubmission for either expedited review or review by convened IRB.

Research that does not qualify for IRB exemption at UCSD if the research includes the following:

a) More than minimal risk procedures
b) Prisoners unless the research is non-federally supported/conducted and only incidentally includes prisoners
c) In vitro fertilization
d) Deception
e) Decisionally impaired participants
f) The use of school records of identifiable students or interviewing instructors about specific students unless permission from the school district/college/university administration has been obtained before the research is initiated and a copy of the letter of permission has been submitted and accepted by the HRPP Office. The letter must address how Title 34 of the Code of Federal Regulations Part 99 – Family Educational Rights and Privacy Act (FERPA) applies to this research.
g) Survey or interview procedures with children (participants under the age of 18 years)
h) Observation of public behavior when the investigator(s) participates in the activities being observed
i) Data collected that includes protected health or medical information when there is a direct or indirect link that would identify the participant
j) Sensitive aspects of the participant's own behavior, such as illegal conduct, drug use, sexual behavior or use of alcohol
k) FDA research except in emergency circumstances

l) Research that requires review by the UCSD Embryonic Stem Cell Research Oversight (ESCRO) Committee.

Procedures

The IRB Chair or the IRB Chair's designee will determine whether a submitted research project meets the requirements for exemption from IRB review. The IRB Chair or the IRB Chair's designee can require expedited or full review of any research at his/her discretion, even if the research would otherwise qualify for exempt review status. The decision to actually grant exempt review status is initially made by the IRB Chair or the IRB Chair's designee, who must review the full set of documents submitted by the investigator in reaching a decision during an exempt review.

The Principal Investigator must submit the following documents to the HRPP for consideration of exempt review: Cover Sheet for Exempt Status Application; Exempt Status Facesheets including appropriate signatures; Research Plan for Exempt Categories 1, 2, and 3 or Research Plan for Exempt Category 4; additional protocol materials such as consent, survey, interview questions, etc., as needed; and any other information known to be relevant.

If it is determined that exempt review is appropriate for a study or one of the other activities described above and the IRB Chair or the IRB Chair's designee wishes to utilize this procedure, the IRB Chair or the IRB Chair's designee will document his/her determination of risk. The review is then performed by the IRB Chair or the IRB Chair's designee.

The IRB Chair or the IRB Chair's designee will evaluate research determined to be exempt to ensure that it meets University of California, San Diego ethical standards. Such an evaluation might include the following:

1. The research holds out no more than minimal risks to subjects.
2. Selection of subjects is equitable.
3. If there is recording of identifiable information, there are adequate provisions to maintain the confidentiality of the data.
4. If there are interactions with subjects, there will be a consent process that will disclose such information including a) that the activity involves research; b) a description of the procedures; c) that participation is voluntary; d) name and contact information for the investigator; and e) there are adequate provisions to maintain the privacy interests of the subjects. A sample of a consent document/wording is provided here.

When a study has been certified as exempt from IRB review, continuing review and approval is not required. Certification of Exemption is effective for the life of the study.

However, all modifications to a study that has been certified exempt must be submitted to the IRB for prospective review and certification of exemption prior to implementation. In some circumstances, changes to the protocol may disqualify the project from exempt status. Further, investigator responsibilities also include the investigator will following UC San Diego IRB/HRPP policies and procedures for reporting unanticipated problems and deviations.

For projects that include "existing" data, documents, records, pathological specimens, or diagnostic specimens, "existing" is defined as data, documents, records, pathological specimens or diagnostic specimens that exist prior to the date the Exempt Status Facesheets are submitted to the HRPP database. The Research Plan for project associated with existing data, documents, records, pathological specimens, or diagnostic specimens projects will include the specific dates of the records to be reviewed. An amendment may not be used to revise the project to include a later date. If a later date is being requested, a complete "NEW" application must be submitted.

If it is determined that the proposed study is exempt, the Principal Investigator will be provided with a Certificate of Exemption that will include under what category of exemption the study was granted. If it is determined that the proposed study is not exempt *or* additional information is needed to determine exempt status *or* certification is granted pending acceptance of requested modifications/clarifications, the Principal Investigator will be notified of this information in written form.

The IRB is informed of exemption determinations in the summary of HRPP letters and actions since the last meeting that is available as part of the IRB agenda.

Applicable Regulations
21 CFR 56.104(c)
45 CFR 46.101(b)

Links and References
OHRP Human Subjects Regulations Decision Charts
OHRP Guidance on Research Involving Coded Private Information or Biological Specimens
Cover Sheet for Exempt Status Application
Exempt Status Facesheets
Research Plan for Exempt Categories 1, 2, and 3
Research Plan for Exempt Category 4
Sample Informed Consent/Wording for Exempt Project

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

Section 3.10
Expedited Review

Policy

The expedited review process consists of a review of research involving human subjects by the IRB Chair or by one or more experienced reviewers designated by the Chair from among members of the IRB. Such designees must have demonstrated familiarity with the scope of the research as well as a sound grasp of the relevant regulations and policies. Research reviewed by the expedited review process will undergo the same careful review by its reviewer as one subjected to full review; 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.

Categories of Research Appropriate for Expedited Review

New Studies

The categories of research that may be reviewed by the IRB through an expedited review process include research activities that (1) present no more than minimal risk or discomfort to human subjects, and (2) involve only procedures in one or more of the categories listed below. Minimal risk is defined in 45 CFR 46.102(i) and 21 CFR56.102(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.

For projects that include "retrospective" review of records, "retrospective" is defined as data that exists prior to the time of the IRB application submission. The Research Plan for retrospective record review projects will include the specific dates of the records to be reviewed. An amendment may not be used to revise the project to include a later date. If a later date is being requested, a complete "NEW" application must be submitted.

Extended Approval for Studies

UC San Diego's Federal Wide Assurance allows for some flexibility in applying human subjects federal regulations to non-federally funded research. The UCSD IRB/HRPP may grant study approval of up to 3 years (1095 days) for non-exempt studies that satisfy all of the following criteria:

1. The research involves no more than minimal risk to participants.

2 The research does not have direct or indirect federal funding including federal training and program project grants.
3. The research is not subject to FDA oversight.
4. The research does not involve prisoners or parolees.
5. The research is not directed or overseen by a federal agency that has signed on to the Common Rule.
6. The research is not seeking or obtaining a Certificate of Confidentiality.
7. The research has no contractual obligations or restrictions that preclude eligibility in this policy (e.g., the non-federal sponsor or funder of the research requires an annual review).
8. The research is not funded by the California Institute for Regenerative Medicine.
9. The UCSD IRB is not serving as the IRB of record for an institution that applies the federal regulatory standards to all research regardless of the source of funding and/or requires annual review.

If a study becomes ineligible for extended approval, such as by securing new federal funding or other changes, the PI is responsible for promptly submitting an amendment to inform the HRPP of these changes. The HRPP will issue a "new" approval letter with a shortened approval period, as appropriate.

The PI is also responsible for all post-approval submissions even when a project is granted an extended approval. These responsibilities include the following:

1. Amendment request submissions, which must be approved before implementation.
2. Protocol deviations/violation and UPRs submitted per IRB/HRPP SOPP reporting criteria.
3. Continuing Review documents submitted 45 days before the expiration date of the study, if the study is still active.
4. Study Closure documents submitted when study is complete.

<u>Minor Changes in Approved Studies and Informed Consent Documents</u>

In some cases the Chair or Chair's 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. Changes/revisions that involve more than minimal risk or do not fall into Expedited Review categories 1-7 noted above cannot be reviewed using the expedited procedure.

<u>Continuing Review, Interim and Completion Reports</u>

Continuing Review for projects initially approved under expedited procedures is conducted at the intervals not greater than 365 days from the most recent project approval unless the project has been approved for extended approval, in which case intervals will

be not greater than 1095 days. 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.

Modifications Required to Secure Approval

Minor revisions to the informed consent and other documents and clarifications submitted in response to convened IRB review as a condition for approval may be reviewed by expedited review, if determined by the convened IRB at the time of 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, which would require review by a convened IRB.

Modifications in Advertisements

The Chair or Chair's designee may approve minor modifications to approved recruitment advertisements using the expedited review process.

Off-site Safety Reports, Sponsor Provided Annual Reports and Data Monitoring Committee/Data Safety Monitoring Board Reports

The Chair or Chair's designee may review off-site safety reports (including IND safety reports), sponsor provided annual reports, and data monitoring committee/data safety monitoring board reports by expedited review. These reports would typically indicate that no safety issues were found, and the study should continue without modification.

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 and/or affirmation by the PI, 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.

Process for Conducting Expedited Review

The Chair or the Chair's 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 use 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; and informed consent documents, master plan and investigator brochure, 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 (if applicable), supporting documentation from sponsors; drug-related information such as package inserts (if applicable); 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 applicable 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 IRB review. When the Chair or designee discloses any conflict of interest, the Chair or designee cannot participate in the review.

Procedures

1. IRB Administrator or designee will 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; and document discussions of actions in minutes.
2. IRB Chair or designee will confirm and approve determination that submission qualified for expedited review; make and document determination of minimal risk research; and designate an appropriate IRB member (including self) to conduct the expedited review.
3. Designated Reviewer will conduct review (including protocol, informed consent form).

Applicable Regulations

21 CFR 56.110
45 CFR 46.110
http://www.hhs.gov/ohrp/policy/expedited98.html

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

Section 3.11
Continuing Review

Policy

The UCSD HRPP limits all project approvals to an initial approval period of 365 days, and upon continuing review to an additional approval period not to exceed 365 days. After one initial approval and nine continuing review approvals, 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 provide the complete continuing review submission not later than 15 days prior to the continuing review deadline but should be provided 30-45 days prior to deadline to ensure no lapse in approval. 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.

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.

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..

As stated above, when an investigator does not provide continuing review information to the IRB or the IRB has not approved continuation, the IRB must ensure that all activities including recruitment, advertisement, screening, consent, and collection of private identifiable data are stopped. The IRB 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.

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.

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 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 reconsent 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, 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.

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. The assigned primary IRB reviewer leads the discussion regarding the review. All IRB members have access to the information necessary to enable them to conduct a review in enough depth to be able to discuss the protocol at the meeting including the materials listed below.

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

1. Continuing Review Facepages and Narrative Summary of Progress to Date: these documents should contain sufficient information to 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. A copy of the stamped, approved consent and/or assent document(s) 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 description of approved or proposed amendments, including updated Master Protocols, Investigator's Brochures, package inserts as well as minor changes, (if any) and the IRB action on each amendment.
4. The number of subjects enrolled in the study. If a VA study, the number of subjects by gender must be provided.
5. A description of the research findings to date.
6. A description of adverse event reports from investigators, sponsor safety reports (e.g., IND or IDE Safety Reports).
7. Documentation of protocol violations and/or deviations, or non-compliance with applicable regulations.
8. A description of 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.
9. A statement from the investigator that all SAEs and unexpected adverse drug experiences have been reported as required.
10. 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.
11. Any new recruitment documents.
12. 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, the IRB 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.

Procedures

1. IRB Members including Chair will 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; review the consent form and update it if needed based upon review of previous items; review any other pertinent reports in the study file (e.g.: audit reports, correspondence, complaints, etc.); and vote on a category of action.
2. IRB Administrator or HRPP staff designee will check Interim, Renewal and Completion Reports for completeness; make copies of reports available to IRB members prior to next convened meeting; notify members of continuing review actions by the Chair or designee using expedited review process; notify investigators of reapproval and other report submission deadlines; and maintain documentation of any new significant findings relevant to study subjects and how the information was provided.

Applicable Regulations

21 CFR 50.25(b)(5)
21 CFR 56.108(a)(4)
21 CFR 56.108(b)(1)
21 CFR 56.109 (f)
21 CFR 56.110(b)
21 CFR 812.150(a)(6)
45 CFR 46.109(e)
OHRP Guidance: Continuing Review
FDA Guidance: Continuing Review

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

Section 3.12
Protocol Amendments

Policy

All modifications/changes in a project must be received and approved by the Institutional Review Board (IRB) ***before*** they are initiated except where necessary to eliminate apparent immediate hazard to the subject. Requests for approval of modifications/changes may be submitted at any time by the Principal Investigator (PI) during the active, approved period of a study.

The modification is reviewed by the IRB Chair or the IRB Chair's designee and a determination of whether convened IRB review is necessary is made.

A modification/change to a project may require a NEW application when the modification/change is to two or more of the following three items: a) the purpose of the study; b) the population involved in the study; or c) the procedures associated with the study.

Major modifications/changes are reviewed through a convened IRB review process. Examples of modifications considered to be major in nature include 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.

Federal guidelines include that "An IRB may use the expedited review procedure to review…minor changes in previously approved research during the period (of one year or less) for which approval is authorized." [45 CFR 46.110(b)(2)]. The review will be carried out by the IRB Chair or his/her designee(s). If the Chair or designee believes that the "minor" modification is too substantive to receive this type of review, the submission will be referred for convened IRB review. Minor modifications that *may* receive expedited review include minor changes in recruitment materials/procedures; correction of typographical and grammatical errors or editorial revisions that do not change the meaning of the study document; change in compensation for participation if not considered to be coercive; addition of new study site; and translations of materials previously reviewed and approved by the IRB.

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). Any amendment provided under these circumstances must undergo convened IRB review at the earliest

opportunity. The review will also include a determination whether each change was consistent with ensuring the participants' continued welfare.

Changes in study sites, investigators, and/or key personnel must also be reported to the IRB. The submission requesting modifications/changes includes a cover letter, and may involve revised application Facesheets, revised Research Plan and consent documents or use the Cover Letter For Request Change/Modification--Key Personnel Changes Only form. In the case of a change in the PI, the cover letter should be signed by the investigator who holds the approval. In addition, a letter signed by the "new" PI should also be provided that indicates the "new" accepts the role of PI and the responsibilities associated with that role.

Process for Conducting Amendment Requests

When reviewing project amendments, the IRB will assess all of the same criteria for approval that were evaluated during initial review. When an amendment is reviewed at the IRB meeting, 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 or whose expert review is requested. The PI must submit the following materials to the HRPP office to request modifications/changes to an approved study:

1. A cover letter that contains the project number, title, name of principal investigator, and should specifically state that an amendment to the currently approved study is being requested. The cover letter should clearly detail what the modification is, why it is being requested, and any potential changes to risks to subjects, risk/benefit ratio, risk management procedures, etc. If revisions have been made to study documents, the cover letter must provide an outline of those revisions as well as why those revisions are being made. The cover letter must be provided over the PI's signature. It is strongly suggested that the Amendment Request Cover Letter form be used.
2. If a change is only being made to key personnel associated with the study, Cover Letter For Request Change/Modification--Key Personnel Changes Only can be used. This cover letter can be used for making changes to key personnel associated with the study only where those changes do not require revision of the consent/permission/assent form(s) and/or the change is not to the PI of the study. Revised Application Facesheets and Research Plan documents would not be required to be submitted until the next submission of either or both of these documents, when the revised document(s) would need to reflect the current personnel and appropriate information about those personnel.
2. Revised application Facesheets, if applicable. The revised Facesheets must be signed and dated by the PI. If a change in the study PI is being requested, revised application Facesheets reflecting the change in PI that is signed and dated by the incoming PI and Department Chair must be provided.
3. Revised Research Plan, if applicable. Two copies of a revised Research Plan are required. One copy must clearly and specifically highlight all the changes made to the document including additions and deletions by using the track changes function in Microsoft Word (or a similar function in other word processing software), and one clean copy of the document must be submitted.

4. Revised consent/permission/assent forms, if applicable. Two copies of the revised document(s) must be submitted. One copy must clearly and specifically highlight all the changes made to the document including additions and deletions by using the track changes function in Microsoft Word (or a similar function in other word processing software). Consent/permission/assent forms are stamped by the HRPP once they have been approved; therefore, the second copy submitted should be a clean copy of the revised consent/assent with a 2-inch by 2-inch "content free" space on the upper left-hand corner of the first page of the document and the lower right-hand corner on the remaining pages for appropriate placement of the IRB stamp-of-approval.
5. Additional information including updated Master Protocol, Investigator's Brochure, package insert, recruitment flyers, if applicable. Two copies must be provided, one that highlights the changes and one clean copy, as noted above.

The amendment request submission should contain sufficient information to 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. 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 assigned IRB reviewer, or Chair or designee in the case of an expedited review.

Based on its review of the above information, the convened IRB determines for each approved research protocol whether the amendment is approved, requires modifications to secure approval, or is disapproved based on assessment of the amendment risks and benefits. The IRB may also require appropriate changes to the Research Plan and/or informed consent/assent forms 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.

For expedited review, the Chair or designee will determine for each amendment request whether the amendment can be approved or requires modifications to secure approval based on assessment of the project's risks and benefits. Appropriate changes to the informed consent/assent form content and/or Research Plan may also be requested.

Applicable Regulations

21 CFR 50.25(b)(5)
21 CFR 56.108(a)(4)
21 CFR 56.108(b)(1)
21 CFR 56.109 (f)
21 CFR 56.110(b)
21 CFR 812.150(a)(6)
45 CFR 46.109(e)
OHRP Guidance: Continuing Review
Amendment Request Cover Letter form
Cover Letter for Request Change/Modification--Key Personnel Changes Only

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

Section 3.13
Reporting Adverse Events and Unanticipated Problems

Policy

Federal regulations [45 CFR46.103(b)(5) and 21 CFR56.108(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) suggested that subjects were at greater risk than was previously know or recognized, 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 IRB will consider the following definition when determining whether a reported event represents an unanticipated problem involving risks to subjects or others: *Unexpected* (in terms of nature, severity, or frequency) given (a) the research procedures that are described in the protocol-relate documents, such as the IRB-approved research protocol and informed consent document; and (b) the characteristics of the subject population being studied; *Related or possibly related to participation* in the research (in this guidance document, possibly related means that there is a reasonable possibility that the incident, experience, or outcome may have been caused by the procedures involved in the research); and *Suggests that the research places subjects or others at greater risk of harm* (including physical, psychological, economic, or social harm) that was previously know or recognized.

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. Incarceration of a participant in the course of a study.
7. A change in FDA labeling or withdrawal from marketing of a drug, device, or biologic used in a research protocol.
8. 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.
9. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.
10. An event that requires prompt reporting to the sponsor.
11. Sponsor imposed suspension for risk.

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

The convened 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.

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 by the Primary Discussant who will provide assessment of the report. All associated documents will be available for IRB review. 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 IRB. 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. The IRB 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, in compliance with guidance provided by federal regulations and University policy.

Information about serious adverse events *not* deemed to be UPRs at this site needs to be reported at least annually as part of a "re-submission" of the study or Continuing Review submission. The information to be provided regarding non-UPRs includes subject ID; description of event, date of event; any costs (if known); who paid the costs (if known); and PI's assessment of the event (e.g., likelihood the event caused by the study including unlikely and definitely unrelated).

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; however, these events must be reported to the IRB at least annually at the time of 10-year "re-submission" or Continuing Review submission.

Examples

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

1. Any serious accidental or unintentional change to the IRB-approved protocol that involves risk or has the potential to recur.

2. Any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject.
3. 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.
4. Any breach in confidentiality or privacy that may involve risk to a participant or others.
5. Any complaint of a subject that indicates an unanticipated risk (e.g., unexpected side effect) or that cannot be resolved by the research staff.
6. In FDA clinical trials, adverse events that involve participants enrolled at sites under the direct purview of the UC San Diego IRB 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.
7. Any other event that indicates participants or others might be at risk of serious, unanticipated harms that are reasonably related to the research.

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), and the UCSD Institutional Official.

Procedures

1. Principal investigator submits AE and UPR reports in a timely fashion to the HRPP and develops a Research Plan describing data and safety monitoring.
2. IRB Administrator reports UPRs, instance of serious or continuing noncompliance with regulations or committee requirements, to the FDA, OHRP, and other appropriate institutional officials in compliance with federal regulations and institutional policies.

Applicable Regulations, Forms and Links

FDA Guidance for Reporting Adverse Events
Guidance on Reviewing and Reporting Unanticipated Problems Involving Risks to Subjects or Others and Adverse Events
Reporting Unanticipated Problems Involving Risk to Participants or Others (UPRs) to the IRB fact sheet
Decision Tree for Reporting Unanticipated Problems and Adverse Events in Research to the IRB and RCP
Report Of Unanticipated Problem Involving Risk To Subject Or Others form

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

Section 3.14
Protocol and Regulatory Violations and Exceptions

Policy

Federal regulations require that any modification to an approved protocol must be reviewed and approved by the IRB prior to implementing the change except when necessary to eliminate apparent immediate hazards/risks to subjects. Conducting research procedures without IRB approval can negatively impact the rights, welfare, and safety of human subjects who participate in research. Research activities include all aspects associated with the conduct of the research including activities related to recruitment, consent, protection of privacy and confidentiality and all information outlined in the IRB reviewed and approved application/protocol.

Protocol/Regulatory 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, are considered violations and must be reported to the IRB in a timely fashion. Minor violations may be reported to the IRB at the time of continuing review. *Major violations must be reported to the IRB within 10 working days of awareness of the violation.*

Major violations include instances that impact participant safety, substantially alter risks to participants, are non-compliant with applicable UCSD HRPP, federal, state and institutional policies and regulations, or any instance determined by the IRB Chair, HRPP Director or HRPP Associate Director to require review by a convened IRB.

Examples of major violations include but are not limited to any deviation from the protocol taken without prior IRB review to eliminate apparent immediate hazard to a research subject; an event or incident that meets the criteria for an unanticipated problem involving risk to participants or others; a serious accidental or unintentional change to the IRB-approved protocol that alters the level of risk; failure to obtain legally effective informed consent; study procedures that are done that are not approved by the IRB; incorrect research treatment or intervention given to the subject; failure to report serious unanticipated problems/adverse events involving risks to subjects or others to the IRB; failure to perform a required lab test or perform a study visit/study labs during the required time frame, that, in the opinion of the PI, may affect subject safety or data integrity; and loss of adequate resources that affects the protection of the rights and welfare of participants.

Minor protocol violations include instances that do not impact participant safety or substantially alter risks to participants.

Examples of minor violations include but are not limited to failure to perform a required lab test or perform a study visit/study labs during the required time frame, that, in the opinion of the PI, does not affect subject safety or data integrity; over enrollment; and missing lab results.

The IRB shall investigate allegations concerning possible regulatory non-compliance with UCSD HRPP 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 presentation of the allegation to the person(s) involved with a request for a response; review of the problem by the IRB and communication of its recommendations to the investigator; and 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, or UCSD regulations or policies will be reported promptly to the UCSD Institutional Official; the Dean, UCSD School of Medicine; the Office of Human Research Protections (OHRP) and the US FDA (for FDA-regulated test articles), as appropriate.

Serious noncompliance includes noncompliance a) that results in substantive harm or damage (or risk of substantive harm or damage) to the safety, rights, or welfare of human subjects, research staff, or others; or b) substantively compromises the integrity or effectiveness of the research.

Ongoing noncompliance includes a pattern of noncompliance that indicates a deficiency likely to result in further noncompliance (e.g., a pattern that indicates a lack of attention to or knowledge or understanding about regulations or ethics) or a circumstance in which an investigator fails to cooperate with investigating or correcting noncompliance.

For a more detailed description of policies and procedures associated with review of regulatory violations, see SOPP, section 5.2, Communications, Sanctions, Appeals, and Disciplinary Actions.

<u>Protocol Exception to Enroll an Individual Subject</u>
A protocol exception to enroll an individual subject is to allow a one-time enrollment of a single individual who does not meet the inclusion/exclusion criteria of an approved protocol or emergency use criteria (emergency use criteria can be found in SOPP, section 3.5, Emergency Use and Informed Consent). Protocol Exception to Enroll requests should be rare and clearly determined to be in the best interest of the patient.

In order to enroll such a subject, a request must be submitted to the IRB for review and approval. The subject *may not be enrolled* until approval has been granted from a convened IRB. The request must include the following information:

1. Why it is appropriate to enroll this subject is this protocol.
2. What specific study criteria are not satisfied by the subject.
3. Justification of potential risk to the subject.
4. Have other protocol exception(s) been done on this study. If so, provide a brief description of each.
5. Documentation of approval by the study sponsor to provide the exception, as appropriate.
6. Clarification as to whether data collected on this subject will be provided to the study sponsor.
7. Clarification as to whether an amendment to the protocol's inclusion/exclusion criteria will be done. If yes, the timeframe for submitting the amendment to the IRB. If no, justification for not submitting such an amendment including why modifying the inclusion/exclusion criteria are appropriate for this subject and not all potential subjects.

Procedures

1. Submission of Major Protocol Violation and Regulatory Violation Reports to the IRB
    a) The PI submits a report to the IRB outlining any and all Major Protocol Violations and any and all Regulatory Violations to the IRB immediately upon becoming aware of the event but no later than 10 working days. The report should include subject ID; description of event, date of event; any costs (if known); who paid the costs (if known); and the PI's assessment of the event (e.g., risk to subject(s)) as well as what procedures will be done in the future to prevent a similar violation and provide revised study documents, as appropriate.
    b) The PI reports the violations to the sponsor, if applicable, following the sponsor's requirements.
2. Submission of Minor Protocol Violations to the IRB
    a) The PI provides information regarding minor protocol violations at the time of continuing review or study closure on the "Narrative Summary Of Progress To Date" or Narrative Summary of Progress to Date at Study Closure" (as appropriate) form including subject ID; description of event, date of event; any costs (if known); who paid the costs (if known); and the PI's assessment of the event (e.g., risk to subject(s)) as well as what procedures will be done in the future to prevent a similar violation and provide revised study documents, as appropriate.
3. Submission of Protocol Exception requests to the IRB
    a) The PI provides requested information for a protocol exception request to the IRB as soon as possible upon determination that enrollment of subject is in the best interest of the potential subject.
4. Review of Violation Reports submitted to the IRB
    a) Reports regarding protocol/regulatory violations will be reviewed by the IRB Chair, HRPP Director or Associate Director. If the violation is determined to be major or regulatory in nature or appropriate for review by a convened IRB, the report will be placed on a meeting agenda to be reviewed by the IRB at the next appropriate IRB meeting. If the report is determined to be a minor violation, the report may be reviewed using expedited procedures.

b) Reports provided at the time of continuing review will be placed on a meeting agenda to be reviewed by the IRB at the next appropriate IRB meeting as part of the continuing review.
c) Reports provided at time of study closure will be reviewed by the IRB Chair, HRPP Director Associate Director. If the violation is determined to be major or regulatory in nature or appropriate for review by a convened IRB, the report will be placed on a meeting agenda to be reviewed by the IRB at the next appropriate IRB meeting. If the report is determined to be a minor violation, the report may be reviewed using expedited procedures.

5. Review of Protocol Exception Requests
   a) Protocol Exception Requests will be reviewed by the IRB Chair, HRPP Director or Associate Director and will be placed on the agenda of the next appropriate IRB meeting for review by a convened IRB.
6. Review outcomes
   a) The IRB may approve, approve pending, or defer a violation report/protocol exception request.
   b) For Regulatory Violations, the IRB will follow policies and procedures as outlined in SOPP, section 5.2, Communications, Sanctions, Appeals, and Disciplinary Actions.
   c) The IRB will, as appropriate, determine whether the violation constitutes "serious" or "continuing" non-compliance or an "unanticipated problem involving risks to subjects or others." Violation(s) found to describe serious and/or continuing non-compliance or an unanticipated problem involving risks to subjects or others will be reported to various entities as outlined in SOPP, section 5.2 and SOPP, section 3.13, Reporting Adverse Events and Unanticipated Problems, respectively.

Applicable Regulations, SOPPs, and Forms

21 CRR 56.108(a)(4)

45 CFR 46.112

45 CFR 46.113

UCSD SOPP, section 3.5

UCSD SOPP, section 3.13

UCSD SOPP, section 5.2

UCSD Narrative Summary of Progress to Date for Biomedical Studies

UCSD Narrative Summary of Progress to Date for Social and Behavioral Studies

UCSD Narrative Summary of Progress to Date at Study Closure for Biomedical Studies

UCSD Narrative Summary of Progress to Date at Study Closure for Social and Behavioral Studies

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

Section 3.15
Radiation Exposure and Radioisotopes

Policy

All projects, including their amendments, involving radiation exposure at UCSD or VASHDS facilities 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.

The UCSD Human Exposure Review Committee (HERC) approval may be obtained before, during, or after application to the IRB. The IRB has final approval of wording regarding human subject radiation exposure in the consent/assent document.

Investigators will note on the IRB application Facesheets the types of radiation sources proposed for use in the study, and provide in the risk/benefit item of the Research Plan an assessment of the risks of radiation exposure. The Research Plan will be reviewed by both the HERC and IRB. The HERC and IRB will make independent assessments of the risks and benefits of the procedures involving radiation. The review documentation provided by the HERC to the IRB will be incorporated into the archival project file and may at the discretion of the IRB be provided to the PI in association with the IRB's comments and requests.

Interactions between the HERC and the 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 HERC. The online interface also provides to the HERC copies of all correspondence issued by the IRB relevant to a research project.

Procedures

1. HRPP staff will determine the existence of radiation use in protocol submissions, route proposals to the appropriate radiation safety committee so that findings and feedback may be provided to investigators.

Applicable Regulations

21 CFR 56.108(A)(1-2)
21 CFR 812.2(b)(1)(ii)
21 CFR 812.66
45 CFR 46.109
45 CFR 46.111

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

Section 3.16
Registry/Repository/Banking Use of Data/Specimens

Policy

Registries/Repositories involve the collection of data/specimens. A registry is typically considered a collection of data. A repository is typically considered a collection of specimens. Data/Specimens collected and stored for future research purposes are considered "banked." Data/Specimens are not considered to be "banked" (stored) if the data/specimens are used for only the purposes defined in the protocol and are destroyed either when that use is completed or at the end of the protocol.

Research involving the collection of these materials 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 typically requires convened IRB review.

IRB Review Procedures

The IRB will consider the application by means of a convened IRB or an expedited 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. The purpose of the registry/repository/banking use of the data/specimens.
2. The data/specimens that will be collected.
3. Procedures for the collection of the data/specimens including from whom the data/specimens will be collected, whether the data/specimens will be collected during research or clinical procedure(s) or both, etc.
4. The risks associated with registry/repository/banking including risk of re-identification.
5. The specific methods for protection privacy and confidentiality of data/specimens collected as well procedures to minimize any other risks associated with registry/repository/banking including re-identification.
6. The procedures associated with obtaining informed consent/permission/assent. If appropriate, these procedures should include the re-consenting a child when the child becomes an adult and/or for each use of data/specimens. If a waiver of consent/assent is requested, justification for the granting of such a waiver must be provided.
7. The procedures for contacting participants in the future, if appropriate.
8. The procedures for withdrawing data/specimens by participants. If data/specimens cannot be withdrawn, justification must be provided.

9. Whether results from research done in association with the data/specimens will be disclosed. If so, the procedures for providing the information must be described including to whom and when the findings will be disclosed, scientific validity and need for confirmation, risks and risk management procedure to minimize those risks such as referral to geneticist and/or other specialist. If not, justification for not providing results must be provided.
10. The conditions/procedures for release of data/specimens to "other" investigators provided, if appropriate. Note: if this is a NIH-funded research for which the NIH Genomic Sharing (GDS) Policy applies, see below.
11. Whether an advisory committee for the distribution of data/specimens is associated with the study. Is so, a description of the committee and their procedures must be provided.

National Institutes of Health (NIH) Genomic Data Sharing (GDS) Policy

As noted by NIH guidelines, "The GDS Policy applies to all NIH-funded research that generates large-scale human or non-human genomic data as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, metagenomic, epigenomic, and gene expression data, irrespective of funding level and funding mechanism (e.g., grant, contract, cooperative agreement, or intramural support)."

If a study is subject to the GDS Policy, the Research Plan must include a specific genomic data sharing plan. This plan must clearly indicate how the GDS Policy expectations will be satisfied as well as "denote the type(s) of data to be submitted, which data repository(s) data will be submitted to, the appropriate uses of the data (i.e. data use limitations), and the data sharing timeline."

Further, in regards to risks of participant identification, the guidelines include, "The GDS Policy stipulates that human data submitted to NIH-designated data repositories, such as dbGaP, are to be coded and de-identified by the submitting investigator, and the key to the code that links the data to specific individuals held by the institution. In order to minimize the risk that research participant identities could be readily ascertained, data should be de-identified by standards consistent with both HIPAA and the Common Rule." The Investigator must ensure the Research Plan addresses these issues, as appropriate.

Guidelines also note "An Institutional Certification stipulating the appropriate uses of data submitted should be provided by the Authorized Institutional Official(s) of the submitting institution prior to award of funding (or the start of research for NIH intramural investigators) when genomic data generation is proposed. The purpose is to assure that submission of data to an NIH-designated data repository is consistent with the GDS Policy and with the informed consent of the original study participants." It is the Investigator's responsibility to ensure the submission provides sufficient information to allow for the verification of information included on the Certification. Fillable Institutional Certification Forms are available on the GDS website at https://gds.nih.gov/Institutional_Certifications.html.

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 are 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 data/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 wishes to withdraw consent for the use of the data/specimen, this may be done at any time without penalty or loss of benefits to which the participant is otherwise entitled, and in this event, the data/specimen will be withdrawn, if possible, but the data/specimen already distributed for research use will not be retrieved.
4. That refusal to participate does not affect the subject’s ability to participate in any associated 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 by including a “Moore clause.”
7. If the investigator has any commercial interest from which he/she may benefit financially, directly or indirectly.
8. If the data/specimen will be used for future research and to allow the subject the choice of how the data/specimen will be used. Federal guidelines include the

following: “When considering the use of a tiered or specific consent approaches, investigators should balance responsibility of protecting participants’ interests with the potential loss of opportunities for public benefit due to limitations on future research uses.” The consent should clarify the present and future uses of the participant’s data/specimens. The consent may provide subjects with broad wording of the future use of the data/specimens or wording with sufficient number of options. Options might include the following:

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.

9. Information regarding the California Genetic Information Nondiscrimination Act (CalGINA).
10. The possibility of “re-identification” of “de-identified” data that could potentially be used to discriminate against or stigmatize participants, their families, or groups. In addition, there may be unknown risks.
11. There will be no direct benefit to the participant from secondary research that may be conducted.

The National Human Genome Research Institute provides an excellent resource for wording that may be used in the consent to address these various elements including wording for “broad versus a specific consent…considerations for families…considerations for identifiable populations…studies involving children…studies involving participants who cannot give consent…data and sample sharing through data repositories and biobanks…return of results and incidental findings to participants.” This resource can be found at https://www.genome.gov/27559024/informed-consent-special-considerations-for-genome-research/.

Reuse and Storage of Data/Specimens

Reuse of data/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 data/specimens are sent to an entity outside of UCSD for testing or use as defined in an IRB-approved protocol, an appropriate agreement must be in place between the outside entity and UCSD. The agreement may include specific use of the specimen as defined in the protocol and/or destruction of specimens or return of specimens to UCSD, as appropriate. This may occur through a Material Transfer Agreement (MTA) of UCSD.

The minimal amount of person-identifiable data necessary should be shared with outside entities, 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 for testing or use, the UCSD investigator must obtain IRB approval 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.

Applicable Regulations

45 CFR 46.110
OHRP Guidance on Research Involving Coded Private Information or Biological Specimens
National Institutes of Health Genomic Data Sharing
The National Human Genome Research Institute

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

Section 3.17
Advertisements, Recruiting Materials, and Procedures and Procedures Preparatory to Research

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 in 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.

Advertisements and Recruitment Materials

Guidance from the FDA includes the "FDA believes that any advertisement to recruit subjects should be limited to the information prospective subjects need to determine their eligibility and interest. When appropriately worded, the following items may be included in advertisements. It should be noted, however, that FDA does not require inclusion of all of the listed items:

1. The name and address of the clinical investigator and/or research facility;
2. The condition under study and/or the purpose of the research;
3. In summary form, the criteria that will be used to determine eligibility for the study;
4. A brief list of participation benefits, if any (e.g., a no-cost health examination);
5. The time or other commitment required of the subjects; and
6. The location of the research and the person or office to contact for further information."

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.

Institutional Review Board 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 the following:

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 will 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. The IRB will 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.
6. Include compensation for participation in a trial offered by a sponsor to involve a coupon good for a discount on the purchase price of the product once it has been approved for marketing.
7. Make claims, either explicitly or implicitly, about the drug, biologic or device under investigation that are inconsistent with FDA (or equivalent regulatory body) labeling.

Advertisements may state that participants will be compensated, but should not emphasize the compensation or the amount to be compensation, 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.

Compensation

When the IRB evaluates the selection of participants and procedures for retaining enrollees, the IRB also considers the influence of compensation. Compensation should be appropriate for the level of risk, discomfort, and/or inconvenience experienced by the participant and not have the potential for coercion or undue influence for a participant to enroll in or remain on the study. The PI must present justification that the compensation offered through these procedures is not inequitable (see also SOPP, section 3.2, Full IRB Review).

Lotteries, Raffles, and Drawings

According to the California Department of Consumer Affairs, "California law prohibits lotteries. A lottery is any scheme for the disposition of property by chance among persons who have paid or promised to pay any value for the chance of obtaining the property, with the understanding that it will be disposed of by chance." (There are three exemptions to this prohibition including the California State Lottery, bingo for charitable purposes and a raffle conducted by a non-profit, tax-exempt organization for charitable purposes.) "Courts have used certain rules to decide whether a scheme includes consideration because it is not always clear. If a person is eligible to win a prize without purchase, there is no consideration and the contest is legal. In such a case, if some people *may* pay money - for example, an admission charge or a product - there is not necessarily consideration if other people may enter without such a purchase. If eligibility to win a prize is limited to those who have paid money, however, there is consideration. Alternatively, if some persons *must* pay in order to have a chance at a prize while others do not, there is consideration."

In addition, there is concern that most people overvalue their likelihood of winning, and therefore, offering a valuable prize may serve to undermine the process of informed consent.

In light of this information, a convened IRB will on a case-by-case basis determine whether lotteries, raffles, and/or drawings may be used to recruit or retain participants. In order for the IRB to consider approving the use of lotteries, raffles, and/or drawings, the following must be addressed:

1. The study is minimal risk;
2. Appropriate compensation is being offered;
3. The Research Plan must include the following:
    a) Procedures to ensure that any individual who is asked to participate in the research study but declines, who consents/assents to enroll in the study, or who fails to complete the study, will be given equal compensation by having an equal chance of winning. In other words, if an individual is eligible to participate in the study, and therefore the lottery, raffle and/or drawing, they do not have to participate in the study to be eligible to participate in the lottery, raffle, and/or drawing;
    b) Procedures for the inclusion of an individual who is not asked to participate in the study but wishes to be included in the lottery, raffle, and/or drawing;
    c) A fair method of choosing the winner and how the winner will be notified; and
    d) Disclosure of the approximate chance of winning (e.g., no less than 1 in 1000).

This information, along with specifically informing individuals that they are not guaranteed to win any prize in the drawing and that the only compensation they will receive is the "1 in X" chance of winning, must be provided in the consent/assent as well as to those who wish to participate in the lottery but not the research study.

Procedures for Purposes Preparatory for Research

It has been a common practice for clinicians who are also doing research to use medical records they have produced, or the clinical information systems of their organization, to identify potential participants for research studies or to find cases for a retrospective chart review. HIPAA distinguishes between the use of medical records for health care — which is a HIPAA covered function — and the use of records for research purposes — which is not covered and must be done only with signed authorization or with a waiver of authorization granted by an Institutional Review Board.

The HIPAA Privacy Rule permits use of PHI for *reviews preparatory to research* however in the University of California system, this is considered part of the overall research plan and requires IRB review prior to the review activity commencing. It is not permissible to begin the research by gathering preliminary data via lookups in clinical information systems, or reviewing clinic appointment logs or other records of clinical care, prior to IRB review and approval of a study.

If procedures for purposes preparatory to research involve review of private information, such as preparing a research protocol, assisting in the development of a research hypothesis, or aiding in research recruitment, for instance identifying prospective research participants who meet the eligibility criteria for enrollment review, consent must be obtained or a waiver of consent must be granted. In order to grant a waiver of consent, this item must clearly describe:

1. Justification why using these procedures would be considered minimal risk to the potential subjects.
2. Justification why a waiver of consent would not adversely affect the rights and welfare of the potential subjects.
3. Justification why these procedures could research not practicably be carried out without the waiver.
4. Whenever appropriate, a procedure for providing potential subjects with additional pertinent information after participation.

If the procedures also include access to PHI, HIPAA authorization must be obtained, or a partial waiver of individual HIPAA authorization must be granted. In order for a partial waiver of HIPAA authorization to be granted, this item must also clearly describe:

1. A plan to a) protect identifiers from improper use and disclosure; and b) destroy identifiers at the earliest opportunity or provide justification for retaining the identifiers;
2. Justification as to why these procedures could not a) practicably be done without the waiver, and b) be done without access to, use, or disclosure of the PHI;
3. Justification that the privacy risk to individuals whose PHI will be used or disclosed is minimal and reasonable in relation to the anticipated benefit, if any, to the individuals; and
4. What PHI will be used and who will access, use or disclose the PHI.

More information about HIPAA and Research at the University of California can be found here.

Note that for studies that involve an FDA-regulated agent, procedures performed in preparation of a clinical investigation would not fall under the definition of a clinical investigation and would not require informed consent.

Procedures

1. IRB members and/or HRPP program staff will review recruitment material, recruitment procedures, and procedures preparatory to research for compliance with applicable policies.

Applicable Regulations and Information Sheet

21 CFR 50.20
21 CFR 312.7(a)
21 CFR 812.7(a)
45 CFR 46.116
UCSD HRPP/IRB SOPPs, section 3.2, Full IRB Review
State of California, Department of Consumer Affairs, Legal Guide U-2 — Rules Prohibiting Lotteries
FDA Recruiting Subjects — Information Sheet
NIH, IRB, and the HIPAA Privacy Rule

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

Section 3.18
Review of Subject Complaints/Concerns/Questions

Policy

The right of research subjects to complain, voice a concern, or ask a question about a research study and to have the complaint, concern or question resolved in a timely manner is taken very seriously by the UCSD Human Research Protections Program. Complaints/Concerns/Questions may be raised by research subjects (past, present and potential), family members, designated spokespersons or anyone and provided to the HRPP by phone, in writing or in person. Consent documents approved by the IRB include information for contacting the Principal Investigator should the subject have questions or research-related problems and for contacting the HRPP Office if the subject has questions about the subject's rights as a research subject or to report research-related problems.

Procedures

1. Principal Investigator Responsibilities/Procedures
    a) The Principal Investigator will address complaints/concerns/questions received from subjects or others as quickly as possible.
        1. If the complaint/concern of a subject or others indicates an unanticipated risk or a change in the risk/benefit ratio associated with the study or the complaint/concern cannot be resolved by the Principal Investigator, it must be reported as an unanticipated event involving risks to subjects or others up with 10 working days (see SOPP, Section 3.13, Reporting Adverse Events and Unanticipated Events Involving Risks to Subjects or Others).
        2. If the complaint/concern does not indicate an unanticipated risk or a change in the risk/benefit ratio associated with the study or the complaint/concern can be resolved by the Principal Investigator, the information associated with the complaint/concern will be included as part of the continuing review submission for review by the IRB.
    b) The Principal Investigator is responsible for ensuring the IRB-approved consent documents contain accurate information for contacting the Principal Investigator should the subject have questions or research-related problems and contact information for the HRPP should the subject have questions about the subject's rights as a research subject or to report research-related problems.
2. HRPP Responsibilities/Procedures
    a) The HRPP Director, or when the Director is unavailable, an HRPP Associate Director, is responsible for initial review of the complaint/concern/question and communicating with person with the complaint/concern/question.
        1. The Director will obtain and document the following information, as appropriate:

a) The person's name and contact information (address, phone number, e-mail address). Collection of this information is not mandatory. However, if the person wishes to remain anonymous, the person will be advised that a thorough review may not be possible and that without this information, follow-up with the person would not be feasible.)
b) The HRPP project number and name of the Principal Investigator
c) The person's relationship to the study such as past participant, present participant, potential participant, participant family member, etc.).
d) A detailed explanation of the complaint/concern/question.
e) Who the person has contacted regarding the complaint/concern/question such as the Principal Investigator, research staff or anyone else and when such contact was made.
f) A description from the person of a proposed resolution of the complaint/concern, if the person has such a proposal.

2. The Director will communicate to the person that he/she will inquire into the circumstances associated with the complaint/concern/question and that a response regarding the resolution of or a determination about the complaint/concern/question will provided to the person along with an approximate estimate of when the response will be provided. The Director will also inform the person about the limits of confidentiality in regards to the inquiry including who may be informed, what information may be reviewed, etc.
3. The Director will review study documents and other relevant information to begin the initial review of the complaint/concern/question. The Director may also contact the Principal Investigator, either verbally or in writing, to obtain information in association with the initial review.
4. After performing the initial review, the Director will determine whether the complaint/concern/question is minor and can be handled administratively or whether the complaint/concern/question needs to be reviewed by the IRB Chair and/or the IRB.
    a) If the complaint/concern/question is determined to be minor including those that do not involve potential risk to subjects or others or cause a change in the risk/benefit ratio associated with the study such as the subject not receiving approved compensation for participation, the review and response for such complaints/concerns/questions may be done at the administrative level by the HRPP Director. The written report associated with the complaint/concern/question and response including corrective action will be made a part of the project file and need not be provided to the appropriate IRB Chair for review.
    b) If the complaint/concern/question is determined to involve potential risk to subjects or others or cause a change in the risk/benefit ratio associated with the study, the written report will be provided to the appropriate IRB Chair for review.
    c) If the complaint/concern/question is determined to be an allegation of noncompliance, the complaint/concern/question will be reviewed as outlined in the SOPP, Section 5.2, Communications, Sanctions, Appeals and Disciplinary Actions.

3. IRB Chair/IRB Review Procedures
   a) After the HRPP Director has provided the report and response regarding the complaint/concern/question to the IRB Chair, the IRB Chair will do the following:
      1. If the IRB Chair determines that the complaint/concern/question does not involve potential risk to subjects or others or cause a change in the risk/benefit ratio associated with the study, the Chair may accept the report and provide to the HRPP Director written acceptance of the report. The report and acceptance of the report will be made a part the project file.
      2. If the IRB Chair determines that the complaint/concern/question does involve potential risk to subjects or others or cause a change in the risk/benefit ratio associated with the study, the IRB Chair may determine the complaint/concern/question requires review by the full Committee and will return the report and response to the HRPP Director so the report and response may be placed on the next appropriate meeting agenda for IRB review.
      3. If the IRB Chair determines that the complaint/concern/question would have an immediate effect to the health, welfare and/or rights of subjects, the IRB Chair will contact the Principal Investigator of the study to establish procedures for the protection of subjects pending review by the IRB.
      4. If the complaint/concern/question is reported to the IRB by the Principal Investigator, the complaint/concern/question will be reviewed as outlined in SOPP, Section 3.11, Continuing Review; Section 3.13, Reporting Adverse Events and Unanticipated Events Involving Risks to Subjects or Other; Section 3.14, Protocol and Regulatory Violations; and/or Section 5.2, Communications, Sanctions, Appeals and Disciplinary Actions.
      5. If the IRB determines that the complaint/concern/question is an unanticipated problem(s) involving risks to others; serious or continuing noncompliance; or results in suspension or termination of IRB approval, the determination and appropriate information must be reported to the Institutional Official and appropriate federal agencies.
      6. The PI will be informed in writing of the results of the review of the complaint/concern/question by IRB within 10 working days.
4. Complaints/concerns/questions about the HRPP
   a) If the complaint/concern/question does not involve risk to subjects and others, the HRPP Director will review and respond/resolve the complaint/concern/question on a case-by-case basis. The resolution may include changes to the standard operating policies and procedures.
   b) If the complaint/concern/question involve risk to subjects and others, the review/response will be done as noted above.

Applicable Regulations

21 CFR 50.25(a)(7)
21 CFR 56.108(b)
45 CFR 46.103(b)(5)
45 CFR 46.116(a)(7)

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

Section 3.19
Collaboration with other UCSD Committees

Policy

The University of California, San Diego IRBs function independently but in coordination with other UCSD Committees to protect human subjects in research. The IRB makes its independent determination whether to approve or disapprove a protocol based upon whether human subjects are adequately protected.

It should be noted that IRB approval does not constitute funding or other institutional required approvals. Should the study involve other review committees, it is the researchers responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens.

In compliance with 45 CFR 46.112, research "approved by the IRB may be subject to further appropriate review and approval or disapproval by officials of the institution. However, those officials may not approve the research if it has not been approved by an IRB." The following provides examples of IRB collaborating UCSD Committees.

The PRMC

The Moores Cancer Center Protocol Review and Monitoring Committee (PRMC) and the Biomedical Research IRBs share oversight responsibilities for the review of cancer-related human subjects research that is conducted at UCSD, affiliate sites, such as RCHSD, and satellite facilities including UCSD San Diego Cancer Center, and North County Sites. The reviews by the PRMC and IRB are complementary with the PRMC focusing mainly on scientific integrity of proposed translational and clinical trials and the IRB focusing mainly on the core ethical principles as outlined in the Belmont Report and regulatory criteria for approval as outlined in 45 CFR 46 and 21 CFR Part 50 and 56. In addition, the PRMC is responsible largely for administrative oversight issues related to feasibility, prioritization, and scientific progress; whereas, the IRB is responsible largely for local context including recruitment and consent procedures, indemnification for research-related injury and informed consent language and documentation. The PRMC and IRB reviews may necessarily overlap in some areas, such as in evaluating the safety of a proposed investigational drug use, the appropriateness of eligibility criteria and safety monitoring, the rationale and ethical justification for experimental interventions vs. available standard-of-care treatments (i.e., equipoise), and in a global risk/benefit assessment.

Procedures for review of cancer-related human research

1. The IRB Biomedical Research Application Facesheets include resources to indicate whether the proposed project will recruit patients with cancer or at a high risk of

developing cancer during the study. The Biomedical Application Research Plan includes an item that provides supplemental instructions for cancer-related studies including that appropriate documents for cancer-related studies should be uploaded to the ePRMC website when the study is submitted to the HRPP.

2. Studies that are eligible for expedited IRB review are typically not required to undergo PRMC review. However, once the review process begins, information provided in response to HRPP queries may indicate that the study requires review by the convened IRB. In this case, the study would then require submission to PRMC for their determination regarding the study.
3. Upon notification from the PRMC or the PI that a PRMC-reviewed study that requires review by a convened IRB has received a PRMC determination of "Approved Pending," "Approved," or "Exempt," the study will be assigned by the HRPP Office to the next appropriate IRB meeting agenda. Assignment is contingent upon availability of required expertise and other factors. The project is assigned approximately eight working days before the date of the IRB meeting. Cancer-related studies may be assigned to an IRB agenda after this date with the approval of the oncology IRB Chair. Studies that have received a PRMC determination of "Deferred" will not be scheduled for IRB review until the study has received a PRMC determination of "Approved Pending," "Approved," or "Exempt."
4. The application will be reviewed separately and independently by the PRMC and the IRB. The IRB may request document versions that have been revised in response to PRMC in order to ensure version control.
5. The PRMC comments/determinations will be provided to the PI from the PRMC in the form of a PRMC determination letter. This PI is responsible for notifying the HRPP of the PRMC determination by submitting the PRMC determination letter to the relevant project file using e-IRB services.
6. An HRPP analyst will have access to the ePRMC database in order to access PRMC meeting minutes and to generally facilitate communication between PRMC and HRPP staff for operations purposes. As the PRMC minutes for new IRB applications include a record of PRMC questions and PI responses discussed during the PRMC meeting that are not included in the PRMC determination letter, they will be provided to the IRB as supplementary information for the IRB to consider. The HRPP analyst will provide a copy of the appropriate entry from the PRMC minutes for each new project amongst the administrative notes in the relevant entry on the IRB agenda.
7. The IRB may disapprove, defer, approve with conditions, or approve protocols that are approved by the PRMC.
8. Final IRB approval is contingent upon final PRMC approval, provided that the PI's efforts to secure PRMC approval do not change or otherwise affect the IRB application under consideration. Should changes be made at the behest of PRMC in order to secure their approval, all revised documents should be submitted to IRB for review.
9. The IRB will make the final determination regarding approval of a study.

<u>The HERC</u>

The Human Exposure Review Committee (HERC) is a subcommittee of the Radiation Safety Committee that reviews all uses of radioactive materials or radiation producing equipment

that result in exposure to human subjects. The Human Exposure Review Committee provides a parallel review of research protocols that include human radiation exposure to the review by the IRB.

Procedures for review of research protocols that include human radiation exposure

1. The IRB Biomedical Application Facesheets include resources to indicate whether the proposed project is associated with radiation or radioactivity exposure to study subjects and what the sources of radiation are. If the Facesheets indicate such an association, the HERC is provided with an automatic e-mail notification that includes a project has indicated such an exposure and the project number and project title.
2. The application instructions include various items to describe the use, risks, risk management procedures, etc. radiation/radioactivity related to the study.
3. The Research Plan and consent(s) and other study documents, as appropriate, will be reviewed independently by the HERC and the IRB. The review documentation provided by the HERC to the IRB will be incorporated into the archival project file and may at the discretion of the IRB be provided to the PI in association with the IRB's comments and requests if the HERC review comments have been provided at the time of the convened IRB review.
4. Interactions between the HERC and the IRB are facilitated by a HERC status field and HERC review notes field maintained in the IRB project tracking system. These data can be updated online via a web interface provided to the HERC. The outline interface also provides the HERC copies of all correspondence issued by the IRB relevant to a research project.
5. Should the PI receive information directly from the HERC that affects the study, the PI will provide this information to the IRB and include a study amendment to revise study documents for review by a convened IRB or using expedited review, as appropriate.

More information about the procedures associated with the review of research protocols that include human radiation exposure are outlined in the SOPP, section 3.15, Radiation Exposure and Radioisotopes.

The IRC (The Independent Review Committee — The Conflict of Interest Office)

The Independent Review Committee is "UCSD's independent substantive review committee appointed by the Chancellor to review financial disclosure statements and relevant features of a research project. They function as the principal advisory committee to eth Chancellor for specific conflicts of interest and determines if a potential, perceived, or real conflict of interest exists by virtue of the investigator's financial interests." The Conflict of Interest Office "assists all employees in assessing situations under which their outside financial interests or other personal considerations may compromise or have the appearance of compromising their actions or judgments in the administration, management, or performance of their professional activities at UCSD." The Conflict of Interest Office provides a parallel review of human research protocols to the review by the IRB.

Procedures for review of possible conflict of interest

1. The IRB application Facesheets include resources to indicate whether the proposed project discloses financial interests. If the Facesheets indicate such a disclosure, the Conflict of Interest Office is provided with an automatic e-mail notification that includes a project has indicated a disclosure of financial interest(s) and the project number and project title.
2. The application instructions include an item requiring a description as to whether the PI or any key personnel associated with this study have any financial interests or other "conflicts" related to the study. The application instructions also note that if a conflict is disclosed, appropriate forms must be provided to the Conflict of Interest Office.
3. The Research Plan and consent(s) will be reviewed independently by the Conflict of Interest Office and the IRB. The review documentation provided by the Conflict of Interest Office to the IRB will be incorporated into the archival project file and may at the discretion of the IRB be provided to the PI in association with a convened IRB's comments and requests including an assessment of any disclosure or management of any conflict of interest provided to the PI such as revision to the consent(s) to provide appropriate disclosure of conflict of interest to subjects.
4. Interactions between the Conflict of Interest Office and the IRB are facilitated by a Conflict of Interest status field and Conflict of Interest Office review notes field maintained in the IRB project tracking system. These data can be updated online via a web interface provided to the Conflict of Interest Office. The outline interface also provides the Conflict of Interest Office copies of all correspondence issued by the IRB relevant to a research project.
5. The Conflict of Interest Office may provide to the IRB a copy of the concurrence letter submitted to the PI from the Independent Review Committee. The PI may be asked to confirm that the procedures outlined in the concurrence letter are being followed and submit revised study documents, as appropriate.
6. Should the PI receive information directly from the Conflict of Interest Office that affects the study, the PI will provide this information to the IRB and include a study amendment to revise study documents for review by a convened IRB or using expedited review, as appropriate.

Institutional Biosafety Committee

The UCSD Institutional Biosafety Committee (IBC) responsibilities include "establishing, monitoring, and enforcing policies and procedures for biohazardous materials and/or recombinant DNA including gene transfer clinical trials" and "reviewing and approving use of biohazardous materials and/or recombinant DNA." The IBC provides a parallel review of human research protocols associated with biohazardous materials and recombinant DNA to the review by the IRB.

Procedures for review of projects that may require Institutional Biosafety Committee Review

1. The IRB Biomedical Research Application Facesheets include resources to indicate whether the proposed project is associated with gene therapy, recombinant DNA and/or gene transfer. If the Facesheets indicate such an association, the IBC is

provided with an automatic e-mail notification that includes that a project has indicated such an association and the project number and project title.
2. The application instructions include various items to describe the use, risks, risk management procedures, etc. of gene therapy, recombinant DNA and/or gene transfer related to the study.
3. The Research Plan and consent(s) and other study documents, as appropriate, will be reviewed independently by the IBC and the IRB. The review documentation provided by the IBC to the IRB will be incorporated into the archival project file and may at the discretion of the IRB be provided to the PI in association with the convened IRB's comments and requests including revision to the consent(s), as appropriate.
4. Interactions between the IBC and the IRB are facilitated by an IBC status field and IBC review notes field maintained in the IRB project tracking system. These data can be updated online via a web interface provided to the IBC. The outline interface also provides the IBC copies of all correspondence issued by the IRB relevant to a research project.
5. The IBC may provide a copy of the Biohazard Use Authorization associated with the study or other appropriate documents to the IRB for inclusion in the study file.
6. Should the PI receive information directly from the IBC that affects the study, the PI will provide this information to the IRB and include a study amendment to revise study documents for review by a convened IRB or using expedited review, as appropriate.

The ESCRO Committee

The Embryonic Stem Cell Research Oversight (ESCRO) Committee is "responsible for ethical and scientific review, approval, and disapproval of human embryonic stem cell research projects. The ESCRO Committee provides a parallel review of human research protocols to the review by the IRB.

Procedures for review of studies that involve human embryonic stem cells at UCSD

1. The IRB application Facesheets include resources to indicate whether the proposed project involves human embryonic stem cells, iPS cells, or other pluripotent cells. If the Facesheets indicate such cells are involved, a representative of the ESCRO Committee is provided with an automatic e-mail notification that includes a project has indicated involvement of human embryonic stem cells, iPS cells, or other pluripotent cell and the project number and project title.
2. The Research Plan and consent(s) will be reviewed independently by the ESCRO Committee and the IRB. The ESCRO Committee members have similar access and follow the same procedures for entering their comments into the HRPP database as IRB members.
3. The ESCRO Committee currently includes members that are also members of the IRB. These members are able to provide additional information regarding the ESCRO Committee review of the project, as needed.
4. The review documentation provided by the ESCRO Committee to the IRB will be incorporated into the archival project file and may at the discretion of the IRB be provided to the PI in association with the IRB's comments and requests.

Applicable Regulations and Standard Operating Policies and Procedures

21 CFR Part 50
21 CFR Part 56
45 CFR 46
45 CFR 46.112
UCSD SOPP, Section 1.5, UCSD Institutional Policies
UCSD SOPP, Section 3.15, Radiation Exposure and Radioisotopes
UCSD SOPP, Section 4.2, Categories of Action

Links

The Moores Cancer Center Protocol Review and Monitoring Committee (PRMC)
The Human Exposure Review Committee (HERC)
The Independent Review Committee (IRC — The Conflict of Interest Office)
The Institutional Biosafety Committee (IBC)
The Embryonic Stem Cell Research Oversight (ESCRO) Committee

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

Section 3.20
Confidentiality of Collected Specimens or Data

Policy

Research involving specimens or data 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. Specifically, the federal regulations regarding the criteria for IRB approval of research include, "When appropriate, there are adequate provisions to protect the privacy of subjects and to maintain the confidentiality of data." Researchers and research staff should understand and follow their department, unit, UCSD, the University of California, Rady Children's Hospital – San Diego (RCHSD), the State of California and Federal privacy laws (HIPAA) policies and procedures, as appropriate, to prevent the disclosure, to other than authorized individuals, subjects' personal and confidential information. Additional information regarding privacy and confidentiality of research records can be found in the UCSD SOPP, Section 3.6, Privacy and Confidentiality of Research Records.

At a minimum, the following guidelines and standards should be followed regarding confidentiality of collected specimens or data:

1. Only the "minimum necessary" participant identifiers/sensitive information shall be collected. The minimum necessary standard is derived from confidentiality codes and practices in common use today. It is based on sound current practice that patient identifiers/sensitive information not be used or disclosed when it is not necessary to satisfy a particular purpose or carry out a function.
2. Participant identifiers/sensitive information shall be removed/destroyed as soon they are no longer needed and in accordance with local guidance on records retention. Researchers should have procedures in place to periodically review collected participant identifiers/sensitive information to ensure it is still required to satisfy a particular purpose or carry out a function.
3. Physical access to areas or computers that contain identifiers/sensitive information shall be restricted to authorized personnel.
4. Electronic access to files on computers that contain identifiers/sensitive information shall be restricted to authorized research personnel.
5. Participant identifiers/sensitive information transmitted over public networks must be encrypted.
6. If possible, a subject code should be used to identify subjects on data files rather than direct participant identifiers. A data file is document, either paper or electronic, that contains information collected as a result of research procedures. The document linking participants and subject code shall be kept separate either physically or electronically from the data file.
7. If participant identifiers/sensitive information must be retained in the data file because of specific needs of the research study, the investigator should provide appropriate justification for such retention. If the data are electronic, the information should be encrypted during storage and decrypted only when needed for the conduct of the study. Justification for retention may include

circumstances where retaining identifiers are necessary for research procedures and subject well being.

8. Participant identifiers/sensitive information should not be stored on portable devices including laptops, USB drives, CD/DVD, smart phones, etc. If it is necessary to use portable devices for the initial collection of identifiers/sensitive information, appropriate protection measures such as encryption must in place before collecting such information and the information must be transferred to a secure system, such as a system that satisfies UCSD Network Security Minimum Standards, as soon as possible.
9. Participant identifiers/sensitive information and contact information may not be distributed outside of UCSD, or its partner institutions, without the specific informed consent of subject, and the approval of the IRB, as appropriate. An approved Data Use Agreement and/or Authorization to transport and utilize VA sensitive information outside protected environments may also be required. Circumstances where such distribution may be allowed include name-based reporting for HIV testing done as part of research or clinical care as codified in the California Code of Regulations for Health Care Providers and Laboratories.

Participant identifiers include the 18 HIPAA "PHI" (protected health information) identifiers and "PII" as defined by California Law SB-1386. The identifiers include names, all elements of dates (except year) for dates directly related to an individual, telephone numbers, fax numbers, e-mail addresses, Social Security numbers, medical record numbers, health plan beneficiary numbers, account numbers, certificate/license numbers and any other unique identifying number, characteristic or code. Sensitive information includes data in any format that requires protection due to the risk of harm that could result from inadvertent or deliberate disclosure, alteration or destruction. The UCSD IRBs consider participant initials to be a participant identifier. Collected information is considered "de-identified" when the above mentioned identifiers have been removed.

Encryption is a process by which information is scrambled so that is it unreadable except to someone who has the "key" to decrypt it. For additional information about encryption and other procedures to address confidentiality associated with participant identifiers/sensitive information, please see the UC San Diego Compliance Program Information Security website and/or the ORO document, Research Information Protection Frequently Asked Questions.

A security breach is when unencrypted PHI, or PII or sensitive information is reasonably believed to have been acquired by an unauthorized person. A suspected security breach means that this information may have been lost or stolen, accessed in an unauthorized fashion or infected by a virus or worm but it is not yet known whether the information has been compromised to meet the level of a security breach.

In the event of a real or suspected breach of security, the appropriate entities should be notified including the UCSDHS Privacy Officer; the UCSD Medical Center Information Security Officer; security@ucsd.edu; the RCHSD Security Officer, as appropriate, and the UCSD HRPP.

Review Procedures

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

1. An full description of what provisions will be used to maintain confidentiality of participant and study data/specimens. This description should include the following, as appropriate:

a) How the participant and study data/specimens will be protected/secured.
b) Who will have access collected information.
c) Who will control access to the information and how will it be controlled.
d) Procedures of "deidentifying" participant and study data/specimens.
e) Procedures associated with removal/destruction of identifiers.

2. Information as to whether it is reasonably foreseeable that the study will collect information that Federal, State, and/or local laws/regulations require reporting to other officials (e.g., child or elder abuse; positive results from lab tests) or ethically requires actions (e.g., suicidal ideation). If such reporting will be done, a description of the reporting procedures/requirements should be provided.
3. Specific information regarding FDA-regulated research, as well as other research, as appropriate, should include the following. The consent form should address these issues, as needed:
    a) When a participant withdraws from a study, the data collected on the participant to the point of withdrawal remain part of the study database and may not be removed.
    b) A researcher may ask a participant who is withdrawing whether the participant wishes to provide continued follow -up and further data collection subsequent to withdrawal from the interventional portion of the study. Under this circumstance, the discussion with the participant must distinguish between study-related interventions and continued follow-up of associated clinical outcome information, such as medical course or laboratory results obtained through non-invasive chart review, and address the maintenance of confidentiality of the participant's information.
    c) If a participant withdraws from the interventional portion of the stud y, but agrees to continued follow- up of associated clinical outcome information, the researcher must obtain the participant's consent for this limited participation in the study (assuming such a situation was not described in the original consent document). IRB approval of consent documents is required.
    d) If a participant withdraws from the interventional portion of a study and does not consent to continued follow-up of associated clinical outcome information, the researcher must not access for purposes related to the study the participant's medical record or other confidential records requiring the participant's consent. However, a researcher may review study data related to the participant collected prior to the participant's withdrawal from the study, and may consult public records, such as those establishing survival status.

Note that OHRP guidelines also include the following: "The expedited review procedure 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."

Informed consent from the subject is generally required for research involving human biological material. In addition to the required and optional elements of informed consent, the informed consent form should contain the following elements regarding confidentiality, if applicable:

1. A full description of what provisions will be used to maintain confidentiality of participant and study data/specimens in lay terms. This description, in lay terms, should include the following, as appropriate:

a) Study procedures associated with the collection of participant/study data/specimens including when the collection will be done, what will be collected, and how confidentiality associated with the information/specimens will be protected/secured.
b) Who will have access collected information/specimens and why such access is required.
c) Who will control access to the information/specimens and how will it be controlled.
d) Whether participant and study data/specimens will be deidentified or collected anonymously.
e) Risks associated with possible inadvertent release/access of collected participant/study information outside the research setting.

2. Information as to whether it is reasonably foreseeable that the study will collect information that Federal, State, and/or local laws/regulations require reporting to other officials (e.g., child or elder abuse; positive results from lab tests) or ethically requires actions (e.g., suicidal ideation). If such reporting will be done, a description of the reporting procedures/requirements should be provided.

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 are 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.

Applicable Regulations

21 CFR 50
21 CFR 56.109
45 CFR 46.110
45 CFR 46.111
OHRP Categories of Research That May Be Reviewed by the IRB through an Expedited Review Procedure
UCSD Health Sciences—Standards of Business Conduct
UC San Diego Compliance Program Information Security Website
UCSD Network Security: Minimum Standards
UCSD HRPP IRB SOPP, Section 3.6, Privacy and Confidentiality of Research Records
University of California Business and Finance Bulletin
California Law SB-1386
California Code of Regulations, Title 17, Division 1, Chapter 4, Subchapter 1
California Code of Regulations, Title 17, Division 1, Chapter 4, Subchapter 1, Article 3.5
ORO Document, Research Information Protection Frequently Asked Questions

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

Section 3.21
IRB Oversight by Non-UCSD "Centralized" IRBs

Policy

As noted by the United States Food and Drug Administration (FDA), "Use of a centralized IRB review process is consistent with the requirements of existing IRB regulations. Section 56.114 (21 CFR 56.114, Cooperative Research) provides that, 'institutions involved in multi-institutional studies may use joint review, reliance upon the review of another qualified IRB, or similar arrangements aimed at avoidance of duplication of effort.'" Further, the FDA notes in the conclusion of the FDA guidance on the use of centralized IRB review, "The Agency hopes that sponsors, institutions, institutional review boards (IRBs), and clinical investigators involved in multicenter clinical research will consider the use of a single central IRB (centralized IRB review process), especially if using centralized review would improve efficiency of IRB review." In addition, Correspondence from the Office for Human Research Protections, dated April 30, 2010, indicates that "the Office for Human Research Protections fully agrees with FDA's position on the benefits of relying on a single central IRB for multicenter research."

The University of California, San Diego, has entered into agreements with non-UCSD IRBs to provide "centralized" IRB oversight for specific types of clinical trials and other research that involves human subjects. The types of research and the procedures for using non-UCSD IRBs are provided below.

UCSD and Western Institutional Review Board (WIRB)

UCSD and WIRB have established an agreement whereby WIRB agrees to assume IRB oversight for some research conducted at or by UCSD. The following describes the scope of research activities for which UCSD will agree to allow WIRB to assume IRB oversight, and outlines the procedures for obtaining permission to submit to WIRB. UCSD has sole discretion on a study-by-study basis for allowing WIRB to assume oversight.

Procedures for Obtaining WIRB IRB Oversight of a Project

WIRB will not review research on behalf of UCSD without notification that the UCSD HRPP has cleared the study for WIRB oversight. The following procedures will be followed:

1. UCSD HRPP staff will screen the application for eligibility for WIRB IRB oversight. Screening involves use of a checklist to ensure that the following criteria are satisfied:
    a) To be eligible for WIRB IRB oversight
        1. The research must be a multi-site (5 sites including UCSD) Phase II, Phase III or Phase IV industry-authored, industry-sponsored, clinical research study or a Phase I industry-authored, industry-sponsored, clinical research study, where the PI has submitted to the UCSD HRPP documentation that the UCSD Institutional Official (IO) for Human Subjects has reviewed the study and is providing discretionary approval for WIRB IRB oversight of the study. This documentation must also include the name of the PI, the title of the study, and the signature of the IO.
        2. The clinical trial agreement must be negotiated through the Office of Clinical Trials Administration (OCTA).

3. Documented approval from the following office:
    i. UCSD Cancer Center Protocol Review and Monitoring Committee (PRMC) review and approval for trials involving patients with cancer or at a high risk of developing cancer during the study.
4. Documented submission of the study for additional review (may be done in parallel), as appropriate:
    i. Conflict of Interest Office/Independent Review Committee review and approval for projects that involve a PI, co-investigator or others associated with the study that have a conflict of interest.

b) Research activities that are not eligible for WIRB IRB oversight
1. Research that has previously received initial review approval from a UCSD IRB.
2. Research on transplant techniques, procedures or other interventions.
3. Research on pregnant women, human fetuses, or neonates.
4. Research involving stem cell therapies.
5. Research involving an infectious agent as the therapeutic agent, gene therapy, recombinant DNA and/or gene transfer.
6. Research involving research-related radiologic procedures unless the radiologic procedures prescribed by the protocol are within the uses in the approved labeling of the radiologic device(s) and are used for standard of care procedures.

c) Submission of completed WIRB specific application Facesheets.
d) Submission of documents outlined on the WIRB Initial Submission Screening Checklist.

2. HRPP staff reviews submitted information and confirms that study is eligible for WIRB IRB oversight and appropriate documents have been submitted. If the study is found to be not eligible or if appropriate documents have not been submitted, the UCSD HRPP will notify the PI in writing. The PI will respond to the HRPP correspondence with the requested action/documents, as appropriate. If the HRPP continues to find the study not eligible or documentation incomplete, the HRPP may decline the request for WIRB IRB oversight and assign the study for review by an appropriate UCSD IRB. If a project has been reviewed by a UCSD IRB, the project may not be submitted to WIRB for review.
3. If HRPP agrees that the study is eligible for reliance on WIRB, a clearance notification ("Clearance") will be sent to the UCSD PI.
4. The UCSD PI submits the study to WIRB according to procedures and requirements agreed to between WIRB and UCSD, with the Clearance attached to the submission.
5. WIRB sends the UCSD PI and UCSD HRPP Institutional Contact e-mail when WIRB has approved the study.
6. UCSD HRPP will contact WIRB to release the approval documentation once approval from OCTA and Office of Coverage Analysis Administration (OCAA) has been provided to the HRPP Office.
7. WIRB approval does not constitute funding or other institutional required approvals. Should a study involve UCSD review committees/department including PRMC, OCTA, OCAA and/or Independent Review Committee, it is the researcher's responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens. If UCSD review committee(s) require revision of the consent/assent, an amendment must be provided to WIRB, and the WIRB fee for review will be paid by the study, per WIRB procedures.

UCSD PI Responsibilities

The PI's responsibilities associated with a study that has received approval from the WIRB IRB:

1. Notify WIRB and the UCSD HRPP of all communication to/from the FDA, OHRP or any other federal, state or local agency regarding a WIRB-approved study.
2. Adhere to UCSD IRB standard policies and procedures (SOPPs) as outlined in this SOPP, WIRB decisions and requirements, and all applicable federal, state, and local laws and regulations regarding the protections of human subjects in research.
3. Submit post-approval WIRB-required forms, reports, notices, and direct communications to WIRB in a timely manner.
4. Assure prompt payment of WIRB submission fees and UCSD HRPP WIRB submission review fee.
5. Submit post-approval amendment requests, unanticipated problems or other events that require prompt reporting and final report directly to WIRB following guidelines provided by WIRB.
    a) For amendments involving consent revision(s), two copies of the revised consent (one copy with the changes underlined or bolded and one "clean" copy) should be submitted to the UCSD HRPP for review *before* submission to WIRB.
    b) For an amendment that involves study staff changes that include the addition of "key personnel," the PI is attesting that the key personnel have completed the appropriate UCSD IRB CITI training.
    c) For all amendments, a copy of the amendment including associated documents and WIRB-approval documentation should be uploaded to the HRPP project number as soon as possible following WIRB approval to ensure appropriate information will be available for UCSD departments/committees including Investigational Drug Service.
6. Submit a copy of the Continuing Review Report provided to WIRB to the UCSD HRPP.
7. Breaches of Confidentiality must also be submitted to the UCSD HRPP as well as other appropriate UCSD Offices including the Office of Research Compliance.
8. The process of study closure will follow WIRB guidelines; however, a copy of the study closure report should also be submitted to the UCSD HRPP.

Notification Requirements Between WIRB and UCSD

In addition to the notification requirements specified in the agreement between WIRB and UCSD, WIRB shall notify the UCSD HRPP Institutional Contact of the following events within the time period specified:

1. Within 24 hours of receipt:
    a) Notifications of imminent harms or threats to UCSD research subjects, staff or faculty.
2. WIRB shall use good faith efforts to provide notice within 24 hours of receipt, but in no event later than five business days from the date of receipt, of the following events:
    a) Notifications of breach of confidentiality of Protected Health Information (PHI) or any other identifiable medical information,
    b) Notifications of an injury or potential injury to a research subject,
    c) Notifications of legal actions or threats of legal actions against UCSD.
3. Within 10 business days:
    a) Determinations of serious or continuing non-compliance, and unanticipated problems,
    b) Subject complaints,

c) Study closure.

Resumption of UCSD IRB/HRPP Oversight

In the event UCSD decides to resume oversight of a study that has been sent to WIRB, or is in the process of being reviewed by WIRB, or has been approved by WIRB:

1. UCSD HRPP will notify WIRB of its decision to resume oversight of the study,
2. UCSD will notify WIRB once the UCSD IRB has approved the research,
3. WIRB may then close out its oversight of the study, as appropriate.

Public Dissemination of Information

Public dissemination of information associated with WIRB-approved studies must be reviewed and approved by the UCSD Communications and Public Affairs Office.

UCSD and The Copernicus Group, Inc. (CGIRB)

UCSD and CGIRB have established an agreement whereby CGIRB agrees to assume IRB oversight for some research conducted at or by UCSD. The following describes the scope of research activities for which UCSD will agree to allow CGIRB to assume IRB oversight, and outlines the procedures for obtaining permission to submit to CGIRB. UCSD has sole discretion on a study-by-study basis for allowing CGIRB to assume oversight.

Procedures for Obtaining CGIRB IRB Oversight of a Project

CGIRB will not review research on behalf of UCSD without notification that the UCSD HRPP has cleared the study for CGIRB oversight. The following procedures will be followed:

1. UCSD HRPP staff will screen the application for eligibility for CGIRB IRB oversight. Screening involves use of a checklist to ensure that the following criteria are satisfied:
    a) To be eligible for CGIRB IRB oversight
        1. The research must be a multi-site (5 sites including UCSD), Phase II, Phase III or Phase IV industry-authored, industry-sponsored, clinical research study or a Phase I industry-authored, industry-sponsored, clinical research study, where the PI has submitted to the UCSD HRPP documentation that the UCSD Institutional Official (IO) for Human Subjects has reviewed the study and is providing discretionary approval for CGIRB oversight of the study. This documentation must also include the name of the PI, the title of the study, and the signature of the IO.
        2. The clinical trial agreement must be negotiated through the Office of Clinical Trials Administration (OCTA).
        3. Documented approval from the following office:
            i. UCSD Cancer Center Protocol Review and Monitoring Committee (PRMC) review and approval for trials involving patients with cancer or at a high risk of developing cancer during the study.
        4. Documented submission of the study for additional review (may be done in parallel), as appropriate:
            i. Conflict of Interest Office/Independent Review Committee review and approval for projects that involve a PI, co-investigator or others associated with the study that have a conflict of interest.
    b) Research activities that are not eligible for CGIRB IRB oversight
        1. Research that has previously received initial review approval from a UCSD IRB.

2. Research on transplant techniques, procedures or other interventions.
3. Research on pregnant women, human fetuses, or neonates.
4. Research involving stem cell therapies.
5. Research involving an infectious agent as the therapeutic agent, gene therapy, recombinant DNA and/or gene transfer.
6. Research involving research-related radiologic procedures unless the radiologic procedures prescribed by the protocol are within the uses in the approved labeling of the radiologic device(s) and are used for standard of care procedures.

c) Submission of completed CGIRB specific application Facesheets.
d) Submission of documents outlined on the CGIRB Initial Submission Screening Checklist.

2. HRPP staff reviews submitted information and confirms that study is eligible for CGIRB IRB oversight and appropriate documents have been submitted. If the study is found to be not eligible or if appropriate documents have not been submitted, the UCSD HRPP will notify the PI in writing. The PI will respond to the HRPP correspondence with the requested action/documents, as appropriate. If the HRPP continues to find the study not eligible or documentation incomplete, the HRPP may decline the request for CGIRB IRB oversight and assign the study for review by an appropriate UCSD IRB. If a project has been reviewed by a UCSD IRB, the project may not be submitted to CGIRB for review.
3. If HRPP agrees that the study is eligible for reliance on CGIRB, a clearance notification ("Clearance") will be sent to the UCSD PI.
4. The UCSD PI submits the study to CGIRB according to procedures and requirements agreed to between CGIRB and UCSD, with the Clearance attached to the submission.
5. CGIRB sends the UCSD PI and UCSD HRPP Institutional Contact e-mail when CGIRB has approved the study.
6. UCSD HRPP will contact CGIRB to release the approval documentation once approval from OCTA and Office of Coverage Analysis Administration (OCAA) has been provided to the HRPP Office.
7. CGIRB approval does not constitute funding or other institutional required approvals. Should a study involve UCSD review committees/department including PRMC, OCTA, OCAA and/or Independent Review Committee, it is the researcher's responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens. If UCSD review committee(s) require revision of the consent/assent, an amendment must be provided to CGIRB, and the CGIRB fee for review will be paid by the study, per CGIRB procedures.

UCSD PI Responsibilities

The PI's responsibilities associated with a study that has received approval from the CGIRB IRB:

1. Notify CGIRB and the UCSD HRPP of all communication to/from the FDA, OHRP or any other federal, state or local agency regarding a CGIRB-approved study.
2. Adhere to UCSD IRB standard policies and procedures (SOPPs) as outlined in this SOPP, CGIRB decisions and requirements, and all applicable federal, state, and local laws and regulations regarding the protections of human subjects in research.
3. Submit post-approval CGIRB-required forms, reports, notices, and direct communications to CGIRB in a timely manner.
4. Assure prompt payment of CGIRB submission fees and UCSD HRPP CGIRB submission review fee.

5. Submit post-approval amendment requests, unanticipated problems or other events that require prompt reporting and final report directly to CGIRB following guidelines provided by CGIRB.
    a) For amendments involving consent revision(s), two copies of the revised consent (one copy with the changes underlined or bolded and one "clean" copy) should be submitted to the UCSD HRPP for review *before* submission to CGIRB.
    b) For an amendment that involves study staff changes that include the addition of "key personnel," the PI is attesting that the key personnel have completed the appropriate UCSD IRB CITI training.
    c) For all amendments, a copy of the amendment including associated documents and CGIRB-approval documentation should be uploaded to the HRPP project number as soon as possible following CGIRB approval to ensure appropriate information will be available for UCSD departments/committees including Investigational Drug Service.
6. Submit a copy of the Continuing Review Report provided to CGIRB to the UCSD HRPP.
7. Breaches of Confidentiality must also be submitted to the UCSD HRPP as well as other appropriate UCSD Offices including the Office of Research Compliance.
8. The process of study closure will follow CGIRB guidelines; however, a copy of the study closure report should also be submitted to the UCSD HRPP.

<u>Notification Requirements Between CGIRB and UCSD</u>

In addition to the notification requirements specified in the agreement between CGIRB and UCSD, CGIRB shall notify the UCSD HRPP Institutional Contact of the following events within the time period specified:

1. Within 24 hours of receipt:
    a) Notifications of imminent harms or threats to UCSD research subjects, staff or faculty.
2. CGIRB shall use good faith efforts to provide notice within 24 hours of receipt, but in no event later than five business days from the date of receipt, of the following events:
    a) Notifications of breach of confidentiality of Protected Health Information (PHI) or any other identifiable medical information,
    b) Notifications of an injury or potential injury to a research subject,
    c) Notifications of legal actions or threats of legal actions against UCSD.
3. Within 10 business days:
    a) Determinations of serious or continuing non-compliance, and unanticipated problems,
    b) Subject complaints,
    c) Study closure.

<u>Resumption of UCSD IRB/HRPP Oversight</u>

In the event UCSD decides to resume oversight of a study that has been sent to CGIRB, or is in the process of being reviewed by CGIRB, or has been approved by CGIRB:

1. UCSD HRPP will notify CGIRB of its decision to resume oversight of the study,
2. UCSD will notify CGIRB once the UCSD IRB has approved the research,
3. CGIRB may then close out its oversight of the study, as appropriate.

Public Dissemination of Information

Public dissemination of information associated with CGIRB-approved studies must be reviewed and approved by the UCSD Communications and Public Affairs Office.

UCSD and Quorum Review Institutional Review Board

UCSD and the Quorum Review IRB have established an agreement whereby the Quorum Review IRB agrees to assume IRB oversight for some research conducted at or by UCSD. The following describes the scope of research activities for which UCSD will agree to allow the Quorum Review IRB to assume IRB oversight, and outlines the procedures for obtaining permission to submit to the Quorum Review IRB. UCSD has sole discretion on a study-by-study basis for allowing the Quorum Review IRB to assume oversight.

Procedures for Obtaining Quorum Review IRB Oversight of a Project

Quorum Review IRB will not review research on behalf of UCSD without notification that the UCSD HRPP has cleared the study for Quorum Review IRB oversight. The following procedures will be followed:

1. UCSD HRPP staff will screen the application for eligibility for Quorum Review IRB oversight. Screening involves use of a checklist to ensure that the following criteria are satisfied:
    a) To be eligible for Quorum Review IRB oversight
        1. The research must be a multi-site (5 sites including UCSD) Phase II, Phase III or Phase IV industry-authored, industry-sponsored, clinical research study or a Phase I industry-authored, industry-sponsored, clinical research study, where the PI has submitted to the UCSD HRPP documentation that the UCSD Institutional Official (IO) for Human Subjects has reviewed the study and is providing discretionary approval for Quorum Review IRB oversight of the study. This documentation must also include the name of the PI, the title of the study, and the signature of the IO.
        2. The clinical trial agreement must be negotiated through the Office of Clinical Trials Administration (OCTA).
        3. Documented approval from the following office:
            i. UCSD Cancer Center Protocol Review and Monitoring Committee (PRMC) review and approval for trials involving patients with cancer or at a high risk of developing cancer during the study.
        4. Documented submission of the study for additional review (may be done in parallel), as appropriate:
            i. Conflict of Interest Office/Independent Review Committee review and approval for projects that involve a PI, co-investigator or others associated with the study that have a conflict of interest.
    b) Research activities that are not eligible for Quorum Review IRB oversight
        1. Research that has previously received initial review approval from a UCSD IRB.
        2. Research on transplant techniques, procedures or other interventions.
        3. Research on pregnant women, human fetuses, or neonates.
        4. Research involving stem cell therapies.
        5. Research involving an infectious agent as the therapeutic agent, gene therapy, recombinant DNA and/or gene transfer.

6. Research involving research-related radiologic procedures unless the radiologic procedures prescribed by the protocol are within the uses in the approved labeling of the radiologic device(s) and are used for standard of care procedures.

c) Submission of completed Quorum Review IRB specific application Facesheets.
d) Submission of documents outlined on the Quorum Review Initial Submission Screening Checklist.

2. HRPP staff reviews submitted information and confirms that study is eligible for Quorum Review IRB oversight and appropriate documents have been submitted. If the study is found to be not eligible or if appropriate documents have not been submitted, the UCSD HRPP will notify the PI in writing. The PI will respond to the HRPP correspondence with the requested action/documents, as appropriate. If the HRPP continues to find the study not eligible or documentation incomplete, the HRPP may decline the request for Quorum Review IRB oversight and assign the study for review by an appropriate UCSD IRB. If a project has been reviewed by a UCSD IRB, the project may not be submitted to the Quorum Review IRB for review.
3. If HRPP agrees that the study is eligible for reliance on Quorum Review IRB, a clearance notification ("Clearance") will be sent to the UCSD PI.
4. The UCSD PI submits the study to Quorum Review IRB according to procedures and requirements agreed to between Quorum Review IRB and UCSD, with the Clearance attached to the submission.
5. Quorum Review IRB sends the UCSD PI and UCSD HRPP Institutional Contact e-mail when Quorum Review IRB has approved the study.
6. UCSD HRPP will contact Quorum Review to release the approval documentation once approval from OCTA and Office of Coverage Analysis Administration (OCAA) has been provided to the HRPP Office.
7. Quorum Review IRB approval does not constitute funding or other institutional required approvals. Should a study involve UCSD review committees/department including PRMC, OCTA, OCAA and/or Independent Review Committee, it is the researcher's responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens. If UCSD review committee(s) require revision of the consent/assent, an amendment must be provided to the Quorum Review IRB, and the Quorum Review IRB fee for review will be paid by the study, per Quorum Review IRB procedures.

UCSD PI Responsibilities

The PI's responsibilities associated with a study that has received approval from the Quorum Review IRB:

1. Notify the Quorum Review IRB and the UCSD HRPP of all communication to/from the FDA, OHRP or any other federal, state or local agency regarding a Quorum Review IRB - approved study.
2. Adhere to UCSD IRB standard policies and procedures (SOPPs) as outlined in this SOPP, Quorum Review IRB decisions and requirements, and all applicable federal, state, and local laws and regulations regarding the protections of human subjects in research.
3. Submit post-approval Quorum Review IRB-required forms, reports, notices, and direct communications to Quorum Review IRB in a timely manner.
4. Assure prompt payment of Quorum Review IRB submission fees and UCSD HRPP Quorum Review IRB submission review fee.

5. Submit post-approval amendment requests, unanticipated problems or other events that require prompt reporting and final report directly to the Quorum Review IRB following guidelines provided by Quorum Review IRB.
    a) For amendments involving consent revision(s), two copies of the revised consent (one copy with the changes underlined or bolded and one "clean" copy) should be submitted to the UCSD HRPP for review *before* submission to the Quorum Review IRB.
    b) For an amendment that involves study staff changes that include the addition of "key personnel," the PI is attesting that the key personnel have completed the appropriate UCSD IRB CITI training.
    c) For all amendments, a copy of the amendment including associated documents and Quorum Review IRB-approval documentation should be uploaded to the HRPP project number as soon as possible following Quorum Review IRB approval to ensure appropriate information will be available for UCSD departments/ committees including Investigational Drug Service.
6. Submit a copy of the Continuing Review Report provided to Quorum Review IRB to the UCSD HRPP.
7. Breaches of Confidentiality must also be submitted to the UCSD HRPP as well as other appropriate UCSD Offices including the Office of Research Compliance.
8. The process of study closure will follow Quorum Review IRB guidelines; however, a copy of the study closure report should also be submitted to the UCSD HRPP.

Notification Requirements Between the Quorum Review IRB and UCSD

In addition to the notification requirements specified in the agreement between the Quorum Review IRB and UCSD, the Quorum Review IRB shall notify the UCSD HRPP Institutional Contact of the following events within the time period specified:

1. Within 24 hours of receipt:
    a) Notifications of imminent harms or threats to UCSD research subjects, staff or faculty.
2. The Quorum Review IRB shall use good faith efforts to provide notice within 24 hours of receipt, but in no event later than five business days from the date of receipt, of the following events:
    a) Notifications of breach of confidentiality of Protected Health Information (PHI) or any other identifiable medical information,
    b) Notifications of an injury or potential injury to a research subject,
    c) Notifications of legal actions or threats of legal actions against UCSD.
3. Within 10 business days:
    a) Determinations of serious or continuing non-compliance, and unanticipated problems,
    b) Subject complaints,
    c) Study closure.

Resumption of UCSD IRB/HRPP Oversight

In the event UCSD decides to resume oversight of a study that has been sent to the Quorum Review IRB, or is in the process of being reviewed by the Quorum Review IRB, or has been approved by the Quorum Review IRB:

1. UCSD HRPP will notify the Quorum Review IRB of its decision to resume oversight of the study,

2. UCSD will notify the Quorum Review IRB once the UCSD IRB has approved the research,
3. The Quorum Review IRB may then close out its oversight of the study, as appropriate.

Public Dissemination of Information

Public dissemination of information associated with Quorum Review IRB-approved studies must be reviewed and approved by the UCSD Communications and Public Affairs Office.

UCSD and National Cancer Institute Central Institutional Review Board (CIRB)

UCSD and CIRB have established an agreement whereby CIRB agrees to assume IRB oversight for some cancer research conducted at or by UCSD. The following describes the scope of research activities for which UCSD will agree to allow CIRB to assume IRB oversight, and outlines the procedures for obtaining permission to submit to CIRB. UCSD has sole discretion on a study-by-study basis for allowing CIRB to assume oversight.

Procedures for Obtaining CIRB IRB Oversight of a Project

Projects that can be reviewed by the CIRB cannot be submitted to the CIRB without notification from the UCSD HRPP that the project has cleared the study for CIRB oversight. The following procedures will be followed:

1. UCSD HRPP staff will screen the application for submission to the CIRB for IRB oversight. Screening involves use of a checklist to ensure that the following criteria are satisfied:
    a) To be eligible for CIRB IRB oversight:
        1. The research must be on the list of CIRB reviewed projects that is available on the CIRB website.
        2. Documented approval from the following office:
            i. Office of OCAA.
        3. Documented submission of the study for additional review (may be done in parallel), as appropriate:
            i. Conflict of Interest Office/Independent Review Committee review and approval for projects that involve a PI, co-investigator or others associated with the study that have a conflict of interest.
    b) Submission of completed CIRB specific application Facesheets.
    c) Submission of documents outlined on the CIRB Initial Submission Screening Checklist.
2. HRPP staff reviews submitted information and confirms that study is eligible for CIRB IRB oversight and appropriate documents have been submitted. If the study is found to be not eligible or if appropriate documents have not been submitted, the UCSD HRPP will notify the PI in writing. The PI will respond to the HRPP correspondence with the requested action/documents, as appropriate. If the HRPP continues to find the study not eligible or documentation incomplete, the HRPP may decline the request for CIRB IRB oversight and assign the study for review by an appropriate UCSD IRB.
3. If the project includes procedures for purposes preparatory to research involving review of private information, such as preparing a research protocol, assisting in the development of a research hypothesis, or aiding in research recruitment, for instance identifying prospective research participants who meet the eligibility criteria for enrollment review, consent must be obtained or a waiver of consent must be granted. In order to grant a waiver

of consent, the submission of a memo must be done that describes: a) Justification why using these procedures would be considered minimal risk to the potential subjects. b) Justification why a waiver of consent would not adversely affect the rights and welfare of the potential subjects. c) Justification why these procedures could research not practicably be carried out without the waiver. d) Whenever appropriate, a procedure for providing potential subjects with additional pertinent information after participation. The UCSD IRB will determine whether a waiver consent may be granted. Expedited procedures may be used to make this determination.

4. If the procedures also include access to PHI, HIPAA authorization must be obtained, or a partial waiver of individual HIPAA authorization must be granted. In order for a partial waiver of HIPAA authorization to be granted, the memo must also clearly describe: a) A plan to a) protect identifiers from improper use and disclosure; and b) destroy identifiers at the earliest opportunity or provide justification for retaining the identifiers. b) Justification as to why these procedures could not 1. practicably be done without the waiver, and 2. be done without access to, use, or disclosure of the PHI. c) Justification that the privacy risk to individuals whose PHI will be used or disclosed is minimal and reasonable in relation to the anticipated benefit, if any, to the individuals. d) What PHI will be used and who will access, use or disclose the PHI. The UCSD IRB will determine whether a partial waiver of individual HIPAA authorization may be granted. Expedited procedures may be used to make this determination.
5. If HRPP agrees that the study is eligible for reliance on CIRB, a clearance notification will be sent to the UCSD PI that will also include documentation of waiver of consent and/or partial waiver of individual HIPAA authorization, as appropriate.
6. The UCSD PI submits the study to CIRB according to procedures outlined by CIRB.
7. The UCSD PI will submit a copy of the CIRB approval letter and approved consent/assent documents to the UCSD HRPP when CIRB has approved the study.
9. CIRB approval does not constitute funding or other institutional required approvals. Should a study involve UCSD review committees/department including Institutional Biosafety Committee and Human Exposure Review Committee, it is the researchers responsibility to ensure that all approvals are in place prior to conducting research involving human subjects or their related specimens. If UCSD review committee(s) require revision of the consent/assent, an amendment must be provided to CIRB.

<u>UCSD PI Responsibilities</u>

The PI's responsibilities associated with a study that has received approval from the CIRB IRB:

1. Notify CIRB and the UCSD HRPP of all communication to/from the FDA, OHRP or any other federal, state or local agency regarding a CIRB-approved study.
2. Adhere to UCSD IRB standard policies and procedures, CIRB decisions and requirements, and all applicable federal, state, and local laws and regulations regarding the protections of human subjects in research.
3. Following approval for the project by CIRB, submit a copy of the approval documentation from CIRB and a copy of the consent/permission/assent documents that will be used on the study.
4. Submit unanticipated problems or other events that require prompt reporting to CIRB following guidelines provided by CIRB.
    a) The PI notifies the CIRB within 7 days of receipt of information related to serious adverse events that meet the criteria of an unanticipated problem.
        1. Submit a copy of report to the HRPP within the same timeframe.

b) The PI notifies the CIRB within 14 days of receipt of information related to other unanticipated problems and/or serious or continuing noncompliance.
    1. Submit a copy of the report to the HRPP within 10 working day of awareness of the occurrence.
5. For an amendment that involves study staff changes that include the addition of "key personnel," the PI is attesting that the key personnel have completed the appropriate UCSD IRB CITI training.
6. For all amendments, a copy of the amendment including associated documents and CIRB-approval documentation should be uploaded to the HRPP project number as soon as possible following CIRB approval to ensure appropriate information will be available for UCSD departments/committees including Investigational Drug Service.
7. Breaches of Confidentiality must be submitted to the UCSD HRPP as well as other appropriate UCSD Offices including the Office of Research Compliance within 10 working days of awareness of occurrence.
8. Submit a copy of the study closure report to the UCSD HRPP and study closure approval documentation from the CIRB within 30 days.

Applicable Regulations, Guidelines, and Links

21 CFR 56.114
FDA Guidance for Industry – Using a Centralized IRB Review Process in Multicenter Clinical Trials
OHRP Correspondence – Use of a Centralized Institutional Review Board
WIRB website
CIRB website
CGIRB website
Quorum Review website

WIRB Application Facesheets
WIRB Initial Review Checklist
CGIRB Application Facesheets
CGIRB Initial Review Checklist
Quorum Review Application Facesheets
Quorum Review Initial Review Checklist
CIRB Application Facesheets
CIRB Initial Review Checklist

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

Section 4.1
IRB Meeting

Policy

Except when an expedited review process is used, the IRB will review proposed research at convened meetings. Each IRB 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.

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 IRB members or alternate IRB members who will vote. Physicians and Ph.D.-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.

The meeting agenda and the meeting materials will be available to IRB members prior to each meeting via the UCSD IRB website. 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 protocol analyst 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.

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 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.

Procedures

1. IRB Chair and IRB Administrator will schedule meetings.
2. IRB Administrator and IRB staff will distribute notice of meeting and ensure appropriate meeting materials are available to IRB members.
3. Primary and Secondary Reviewers will review all relevant meeting materials, prepare IRB meeting presentation (summary, issues and recommendations) and complete review worksheets.
4. IRB members will review materials for all projects prior to meeting.

Applicable Regulations

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)
45 CFR 46.101(a)
45 CFR 46.107 (e)
45 CFR 46.108 (b)
ICH 3.2-3.5
VHA Handbook 1200.05

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

Section 4.2
Categories of Action

Policy

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

Categories of Action

1. Approved
    a) Action taken if majority of the IRB votes to approve the study.
2. Approval Pending with Conditions
    a) Action taken when minor additional information and/or modifications are required or the IRB is unable to judge the application adequately with the information provided. The PI is informed of the additional information/modifications that are required before approval can be granted. The response provided by the PI to the IRB's conditions will be reviewed as follows:
        1. Response to conditions that require review at a convened IRB meeting.
            a) Action taken if the response is directly relevant to the determinations required by the IRB under 45 CFR 46.111 and/or 21 CFR 56.111 or;
            b) Action taken if the IRB requests the response be reviewed at a convened IRB meeting. If the IRB requests that the same IRB review the response, the response will be assigned for review by that IRB at a subsequent, convened IRB meeting, or under exigent circumstances, may be assigned for review by a different IRB with the approval of the Chair of the IRB that requested the same IRB review the response, the Chair of the IRB accepting the review, and the HRPP Director.
        2. Response to conditions that can be reviewed by the IRB Chair, Primary or Secondary IRB Reviewer, or the IRB Chair's designee under expedited procedures ("Out-of-Committee review").
            a) Action taken if the response is not directly relevant to the determinations required by the IRB under 45 CFR 46.111 and/or 21 CFR 56.111, AND the IRB requires minor additional information and/or specific modification(s). The needed information/revisions are agreed upon at the meeting. The additional information may include confirmation of specific assumptions or understandings on the part of the IRB regarding how the research will be conducted. The specific modifications may include precise language changes to the protocol or consent. The investigator is required to concur and provide the additional information and/or written revision of the document(s).
3. Deferral
    a) Action taken if substantial modification is required, the IRB is unable to judge the application sufficiently because insufficient information was provided, or the IRB was unable to provide

specific changes to the protocol that if made would allow the IRB to make the required determinations regarding project approval. The study is deferred and the PI is informed of the reason(s) for the action. In order to receive approval for a deferred protocol, the study must be submitted to the same IRB for review at a subsequent, convened IRB meeting, or under exigent circumstances, may be assigned for review by a different IRB with the approval of the Chair of the IRB that deferred the study, the Chair of the IRB accepting the review, and the HRPP Director.

4. Disapproval
    a) Action taken if the risks to the participants outweighs possible benefits or the proposed research does not meet federal criteria for IRB approval even after substantial modifications. A project may be disapproved if a majority of IRB members cast a vote of disapproval. The study is disapproved and the PI is informed of the reason(s) for the action. In order to receive approval for a disapproved protocol, the study must be re-written and submitted to the same IRB, if possible, for review at a subsequent, convened IRB meeting. The PI may also be given the opportunity to respond in person at the discretion of the IRB and IRB Chair.

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 other appropriate institutional committees may also be required before the research can actually begin.

The approval period will expire exactly 365 days from the date of the most recent convened IRB meeting at which the project was reviewed (not 365 days 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 may be used. Beyond this date, study approval expires. If the IRB has not reviewed and approved a research study by the study's current expiration date, i.e., IRB approval has expired, research activities should stop including recruitment, screening and enrollment of new subjects; continuation of research interventions or interactions with currently participating subjects; and data analysis. The PI will immediately submit to the IRB Chair a list of research subjects who could be harmed by stopping study procedures. The IRB Chair will determine if subjects on the list may continue participating in the research interventions or interactions.

When a project undergoes annual continuing review and is approved for continuation, the approval is for 365 days after the date of the most recent review of the study at a convened IRB meeting (not 365 days from the continuing review approval release date). However, OHRP permits the IRB to re-approve the research up to 30 days prior to the continuing review expiration and still maintain the same date for the Continuing Review approval.

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

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, where appropriate, in a timely manner.

Procedures

1. The IRB reviews and determines the appropriate action, noted above, regarding the project under review.
2. The IRB Chair, HRPP Director and/or an Associate Director will review the response provided by the PI regarding projects determined to have approval pending conditions.
    a) If the response is directly relevant to the determinations required by the IRB under 45 CFR 46.111 and/or 21 CFR 56.111 or the IRB requests the response be reviewed at a convened IRB meeting, the response will be placed on the agenda for review at the next appropriate IRB meeting. If the IRB requests that the same IRB review the response, the response will be assigned for review by that IRB at a subsequent, convened IRB meeting, or under exigent circumstances, may be assigned for review by a different IRB with the approval of the Chair of the IRB that requested the same IRB review the response, the Chair of the IRB accepting the review, and the HRPP Director.
        1. If the response is assigned to the same IRB that performed the initial review, the response will be assigned to either the previous Primary Reviewer/Discussant, Secondary Reviewer or IRB Chair who will lead the discussion by presenting his/her findings and recommendations resulting from the review of the response materials.
        2. If the response is assigned to an IRB that did not perform the initial review, the IRB Chair is assigned as the reviewer of the response. The Chair will lead the discussion by presenting his/her findings and recommendations resulting from the review of the response materials. The IRB Chair or a member of the IRB that performed the initial review of the project will be asked to provide a review of the response.
    b) If the IRB requests that the response be reviewed by a convened IRB, the response will be placed on the agenda for review at the next appropriate IRB meeting. The response will be assigned to either the previous Primary Reviewer/Discussant, Secondary Review or IRB Chair who will lead the discussion by presenting his/her findings and recommendations resulting from the review of the response materials.
    c) If the response provides the specific modifications and/or information requested by the IRB and the response is not directly relevant to the determinations required by the IRB under 45 CFR 46.111 and/or 21 CFR 56.111, the response is assigned for review by an IRB Chair, the Primary or Secondary reviewer or the IRB Chair's designee, and the response may be reviewed using expedited procedures.
3. The IRB Chair, HRPP Director and/or an Associate Director will review the response provided by the PI regarding projects determined to be deferred.
    a) The response will assigned to the same IRB that determined the project be deferred unless under exigent circumstances, when the response may be assigned to a different IRB, if the Chair of the IRB that deferred the project, the Chair of the IRB accepting the review, and the HRPP Director have approved review by a different IRB. If the response is assigned to the same IRB, the

response will be assigned to the previous Primary Reviewer/Discussant and/or Secondary Reviewer and/or IRB Chair if the Primary Reviewer/Discussant and/or Secondary Reviewer are not able to review the response. The Primary Reviewer/Discussant, Secondary Review or IRB Chair will lead the discussion by presenting his/her findings and recommendations resulting from the review of the response materials. If the response is assigned to a different IRB for review, the response will be assigned by expertise to the appropriate Primary Reviewer/Discussant and/or Secondary Reviewer. The IRB Chair or a member of the IRB that deferred the project will be asked to provide a review of the response. The Primary Reviewer/Discussant, Secondary Review or and/or IRB Chair will lead the discussion by presenting his/her findings and recommendations resulting from the review of the response materials.

4. The IRB Chair, HRPP Director and/or an Associate Director will review the response provided by the PI regarding projects determined to be disapproved.
    a) The response will assigned to the same IRB that disapproved the study, if possible. If the response is assigned to the same IRB, the response will be assigned to the previous Primary Reviewer/Discussant and/or Secondary Reviewer and/or IRB Chair if the Primary Reviewer/Discussant and/or Secondary Reviewer are not able to review the response. The Primary Reviewer/Discussant, Secondary Review or IRB Chair will lead the discussion by presenting his/her findings and recommendations resulting from the review of the response materials. If the response is assigned to a different IRB for review, the response will be assigned by expertise to the appropriate Primary Reviewer/Discussant and/or Secondary Reviewer. The IRB Chair or a member of the IRB that disapproved the project will be asked to provide a review of the response. The Primary Reviewer/Discussant, Secondary Review or and/or IRB Chair will lead the discussion by presenting his/her findings and recommendations resulting from the review of the response materials. The PI may also be given the opportunity to respond in person at the discretion of the IRB and IRB Chair.

Applicable Regulations

21 CFR 56.110(b)
21 CFR 56.111
45 CFR 46.110(b)
45 CFR 46.111
ICH 3.1.1
ICH 3.3.9

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

Section 5.1
Protocol Audits

Policy

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

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

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, "Communications, Sanctions, Appeals and Disciplinary Actions."

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

Procedures

1. Auditors complete audit report within 10 working days of completing the audit, review all documents for could provide factual information regarding conduct of the study, conform 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, confirmation information about any adverse events that may be reported, obtain information about any adverse events that may not have been reported, and confirm status of project (enrolling, inactive, etc.).
2. IRB members will review the audit report, assess the need for additional information, determine audit conclusion, and vote on remedial action imposed on investigator, as necessary.
3. IRB Administrator will 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 and contact investigator to arrange audit logistics.

Applicable Regulations, References and Forms

21 CFR 56.108(a)(2)
21 CFR 56.109 (f)
38 CFR 16.103(b) (4)(ii)
38 CFR 16.109(e)
45 CFR 46.103 (b)(4)(ii)
45 CFR 46.109(e)
VHA Handbook 1200.05
UCSD On Site Audit Checklist
FDA GCP Audit Guidelines

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

Section 5.2
Communications, Sanctions, Appeals, and Disciplinary Actions

Policy

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

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

The suspension of a protocol is the temporary cessation of some or all research activities. The termination of a protocol is a permanent cessation of all research activity.

Regulatory Noncompliance

Potential occurrences of regulatory noncompliance in research may be revealed by a complainant or through formal and informal monitoring activities. Non-compliance is a failure to follow the regulations or the requirements and determinations of the IRB. The Chair or his/her designee will initially review allegations of noncompliance and determine whether the alleged are non-compliance in fact. If so, a further determination will be made about whether the non-compliance may (1) cause injury to subjects and rise to the level of an unanticipated 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.

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 IRB Administrator and/or Chair will notify the investigator of the error and define corrective action that needs to be taken. The IRB 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.

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 noncompliance. When suspected serious noncompliance is 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. If the IRB Chair suspends research on an urgent basis, the suspension must be reported to and reviewed by the convened IRB.

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

The Chair and HRPP Director will provide IRB 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. If the IRB determines that non-compliance occurred, a determination of whether non-compliance was serious or continuing must also be considered. When the IRB determines that non-compliance was serious or continuing in nature, the IRB may impose or recommend sanctions as described below. All determinations of serious or continuing non-compliance must be reported to appropriate federal agencies and organizational officials in accordance with the reporting requirements detailed below.

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, 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, the FDA when the study involves a drug or device regulated by the FDA, organizational officials including the Institutional Official and the institution employing the investigator.

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.

Notification and Documentation

If the IRB determines that serious or continuing non-compliance has occurred, this must be reported to the UCSD Institutional Official; OHRP, in all cases; the FDA, when research involves drugs and devices regulated by the FDA. For research sponsored by the Department of Defense, serious or continuing non-compliance must be reported to the Department of Defense.

If the IRB has determined 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.

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, 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 IRB should consider whether procedures for withdrawal of enrolled participant took into account their rights and welfare. The IRB needs to consider whether the PI must inform current participants of the termination or suspension including whether such information may relate to the participants' willingness to continue to take part in the research. 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.

Expired, Suspended or Terminated Protocols

The HRPP is responsible for promptly notifying the PI when a study has expired, has been suspended or is terminated. The sponsoring agency, private sponsor, or other Federal agencies must also be informed. The PI, not the IRB, is responsible for reporting expired, suspended, or terminated protocols to the sponsor.

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 to pursue according to institutional and University policies.

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.

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.

Procedures

1. IRB Chair will make an initial evaluation and initiate suspension or take further action as needed.

2. IRB Member will review files and make determination whether serious noncompliance has occurred, determine if harm to subjects has occurred, and suspend or terminate study as needed, and determine plan of corrective action, sanctions, and monitoring plan, as needed.
3. IRB Administrator will notify investigators of minor instances of noncompliance and prepare correspondence to investigators and distribute to relevant parties, as required.

Applicable Regulations
21 CFR 56.113
45 CFR 46.113

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

Section 6.1
e-IRB Submissions and Review

Policy

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

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

1. To improve the efficiency and reduce the burden of the document review process performed by IRB members.
2. To compensate IRB members for their committee work.
3. To reduce the burden upon faculty investigators in the submission of materials necessary for IRB review and ongoing oversight of research projects.
4. To improve the systematic infrastructure of the HRPP office for creating, archiving and providing access to large numbers of research-related documents.
5. To improve the responsiveness of the HRPP office to inquiries and shared oversight issues arising from other organizational units, including research offices of the VA Medical Center, Veterans Medical Research Foundation, Rady Children's Hospital – San Diego, and the federal Office of Human Research Protections.
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.

Procedures

1. IRB Administrator will maintain currency of FDA electronic signature documentation.

Applicable Regulation, and Link

21 CFR 11 Subpart C

http://irb.ucsd.edu/e-IRBmenu.shtml: e-IRB services link on the IRB website.

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

Section 7.1
Multi-Site Studies

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 IRB(s) of record for each participating facility, and, for VA research, applicable Research and Development (R&D) Committees.

Procedures

1. Investigator Responsibilities
    a) Coordinating Facility
        1. If UCSD or the VA is the coordinating facility, the PI must document how 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.
    b) Participating Facilities
        1. The Investigator has the overall responsibility for the conduct of the study at the participating facility.
2. IRB Responsibilities
    a) 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.

3. External (Off-Site) Adverse Event Reporting
    a) 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. 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.

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

Section 8.1
Abbreviations

ADE	Adverse Drug Event/Experience
AE	Adverse Event
CFR	Code of Federal Regulations
COI	Conflict of Interest
CTA	Clinical Trial Agreement
CRA	Clinical Research Associate
CRF	Case Report Form
CRO	Contract Research Organizations
ESCRO	Embryonic Stem Cell Research Oversight
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HDE	Humanitarian Device Exemption
HERC	Human Exposure Review Committee
HRPP	UCSD Human Research Protections Program
HUD	Humanitarian Use Device
IBC	Institutional Biosafety Committee
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IDE	Investigational Device Exemption
IND	Investigational New Drug
IRB	Institutional Review Board
IRC	Independent Review Committee
MTA	Materials Transfer Agreement
NSR	Non-significant Risk
OCGA	Office of Contract and Grant Administration
OHRP	Office for Human Research Protections
PI	Principal Investigator
PRMC	Protocol Review and Monitoring Committee
SAE	Serious Adverse Event
SR	Significant Risk
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

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

Section 8.2
Definitions

Act: 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.

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 365 days 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. (45 CFR 46).

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: 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.

Enrolled: An eligible, appropriately informed individual agreeing to participate in a study. For instance, when an individual signs an informed consent document, that individual is considered enrolled in the study. (https://irb.ucsd.edu/enrollment-definition.shtml)

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)

Generalizable Knowledge: Knowledge obtained from activities designed (with intent) to collect information about some individuals to draw general conclusions about other individuals that are predictive of future events and that can be widely applied as expressed in theories, principles, and statements and that enhance scientific or academic understanding.

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 50, 45 CFR 46). 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 50, 45 CFR 46). 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))

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 (45 CFR 46).

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 the following:

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 1200.05)

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).

Systematic Investigation: Activities that attempt to answer a research question or questions that is methodology driven in that it collects data or information in an organized and consistent way, and the data or information is analyzed in some way, be it quantitative or qualitative data and conclusion or conclusions are drawn from the results.

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 that 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).