

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