



UNIVERSITY OF CALIFORNIA, SAN DIEGO HUMAN RESEARCH PROTECTIONS PROGRAM

Medical Devices

Policy

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 Institutional Review Board (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:

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

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:

- a. A device, other than a transitional device, in commercial distribution immediately before May 28, 1976, when used or investigated in accordance with the indications in labeling in effect at that time.
- b. A device, other than a transitional device, introduced into commercial distribution on or after May 28, 1976, that FDA has determined to be substantially equivalent to a device in commercial distribution immediately before May 28, 1976, and that is used or investigated in accordance with the indications in the labeling FDA reviewed under subpart E of part 807 in determining substantial equivalence.
- c. A diagnostic device, if the sponsor complies with applicable requirements in Sec. 809.10(c) and if the testing: (1) Is noninvasive, (2) Does not require an invasive sampling procedure that presents significant risk, (3) Does not by design or intention introduce energy into a subject, and (4) Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure. Note: In vitro diagnostic (IVD) device research where 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.
- d. A device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, if the testing is not for the purpose of determining safety or effectiveness and does not put subjects at risk.
- e. A device intended solely for veterinary use.
- f. A device shipped solely for research on or with laboratory animals and labeled in accordance with Sec. 812.5(c).
- g. A custom device as defined in Sec. 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

510(k) Device

The FDA notes that a premarket notification, or 510(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:

- a. 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.>").
- b. No comparable device already available.
- c. No exposure to "unreasonable or significant risk of illness or injury."
- d. 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 full 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.

Procedures Associated with the Use of Devices at UCSD Medical Center

Additional procedures are required when an investigational device or HUD is used at UCSD Medical Center. For example, a “new” procedure code may need to be established, and should sponsor representatives be present in the patient care area during a procedure, credentialing and appropriate agreements must be in place. In addition, the Research Plan and consent must clearly reflect any procedures, risks, risk management procedures, etc. associated with the presence of such a representative.

Further, the device may require review by the UCSD Medical Center Technology Assessment Committee (TAC) in order to evaluate the proposed impact to UCSD Medical Center. Though IRB approval may be granted, TAC may place the study on “hold” pending their review and

approval.

For more information about these procedures, review and the use of devices at UCSD Medical Center, contact the Research Compliance Program at rcp@ucsd.edu or (619) 543-5841.

Applicable Regulations

[21 CFR 812](#)

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

[21 CFR 812.66](#)

[21 CFR 814.124\(a\)](#)

[21 CFR 50](#)

[21 CFR 56.107\(e-f\)](#)

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

[21 CFR 56.108\(c\)](#)

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

[21 CFR 56.111](#)

[45 CFR 46.108 \(a\)](#)

[45 CFR 46.103 \(b\) \(4-5\)](#)

[45 CFR 46.107 \(e, f\)](#)

[45 CFR 46.108 \(b\)](#)

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

[45 CFR 46.111](#)

[38 CFR 16.108 \(a\)](#)

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

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

[38 CFR 16.108 \(b\)](#)

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

[38 CFR 16.111](#)

[ICH 3.1](#)

[Federal Food, Drug and Cosmetic Act](#)

[California Health and Safety Code 445](#)

[VHA Handbook 1200.05](#)

Links

<http://www.fda.gov/cdrh/ode/guidance/1668.pdf>- Humanitarian Device Exemption Review Draft Guidelines

<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/cdrh/ode/idepolicy.pdf> - Guidance on IDE Policies and Procedures