

Wayne State University Human Investigation Committee	
SUBJECT	Approved and Unapproved Devices in Research
Section	
Form Date	12/06
Approvals	12/04/06 Office of the General Counsel, 12/19/06 Steering Committee, Administrative Approval 03/08/07

Background

The U.S. Food and Drug Administration (FDA) regulates research involving medical devices. All clinical investigations, proposals and/or protocols involving medical devices must adhere to 21 CFR 50 regarding the protection of human research participants [subjects] and their proper informed consent process and documentation and 21 CFR 56 requirements in order to be reviewed and approved by the Investigational Review Board (IRB). This review and approval must occur before the investigation begins.

An unapproved medical device may only be used on human research participants (subjects) when the device is under clinical investigation and when used by an investigator involved in that study (21 CFR 812); see also Human Investigation Committee (HIC) Policy/Procedure "Emergency/ Single Time Use of Test Article" for exceptions in certain clinical care situations.

Clinical trials using unapproved medical devices on human participants are performed under an Investigational Device Exemption (IDE). Any clinical study that involves a device of significant risk (SR) must be approved by the FDA and by the Wayne State University (WSU) IRB prior to the onset of the study.

The Center for Devices and Radiological Health (CDRH) is the branch of the FDA that is responsible for device studies.

Scope

All device studies at WSU involving human subjects must be submitted to the HIC for review and approval prior to initiation of any study activities. If the study is conducted at the J. D. Dingell Veterans Administration Medical Center (VAMC), the study must be reviewed and approved by the Clinical Investigation Committee (CIC) [VHA Handbook 1200.5 .15(c)] prior to it being sent for review by the HIC. See HIC Policy/SOPs "Emergency/Single Use of Test Articles" for more information.

Definitions

Medical Device – Any health care product that does not achieve its primary intended purpose by chemical action or by being metabolized (e.g., surgical lasers, wheelchairs, sutures, pacemakers, vascular grafts, stents, intraocular lenses, orthopedic pins, diagnostic aids such as reagents and test kits for in-vitro diagnosis of disease and other medical conditions).

Investigational Device – A medical device that is being studied to evaluate its effectiveness and/or its safety. It is considered investigational if it either: 1) is not approved for marketing in the United States or 2) the device is approved for marketing but is being evaluated clinically for a new indication/use.

Significant Risk Device (SR) – A device that may present a potential for serious risk to the health, safety or welfare of a participant and: (1) is intended as an implant; or (2) is used in supporting or sustaining human life; or (3) is of substantial importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health; or (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject is considered a significant risk device [21 CFR 812.3(m)].

Non Significant Risk Device (NSR) – A device that does not meet one or more of the criteria for a significant risk device is considered a non significant risk device. In other words, it is not an implant, not used to support or sustain human life, not of substantial importance in diagnosing, curing, mitigating or treating disease, is not significantly involved in preventing impairment of human health, or does not present a potential risk or serious risk to the health, safety or welfare of a subject [21 CFR 812.2(b)].

Investigational Device Exemption (IDE) – Is granted by the FDA for clinical trials that use unapproved investigational or medical devices on human subjects. This allows the researcher to use a device that has not undergone the appropriate stages to be a FDA approved device. An IDE is required when the unapproved device poses a significant risk to subjects (21 CFR 812.30).

Test Article – any drug, biological product, or medical device for human use, human food additive, color additive, electronic product or any other article subject to regulation under the Federal Food, Drug and Cosmetic Act (21 CFR 50.3(j),) or under sections 351 or 354-360F of the Public Health Service Act (VHA 1200,5 3,y)

Treatment Use (Compassionate) of Investigational Medical Device – Under an existing Investigational Device Exemption the FDA may allow treatment with a medical device of a small number of seriously ill patients who have no other acceptable alternatives. The FDA requires the sponsor/investigator to provide a supplement to an existing IDE justifying the “compassionate use”.

HIC Policy and Procedures

All device studies involving human subjects must be submitted to the HIC for review and approval before the study begins.

All significant risk studies of non-approved devices must receive approval from the FDA and HIC prior to beginning.

The Principal Investigator (PI) must submit sufficient information regarding the device and its intended use to the IRB. The IRB may conduct its own risk assessment, in addition to that of the sponsor and the FDA, if needed.

IDE Guidelines

The PI or sponsor is required to submit an IDE number that has been provided by the FDA for most studies involving devices at WSU.

- An IDE from the FDA is required when the device study involves an unapproved device that poses a significant risk to participants [21CFR 812.2(c)].
- An IDE is required when a significant risk study is testing an FDA-approved device for a new indication.

If the PI holds the IDE and not a sponsor, the PI must assume the functions of the sponsor. In this case, the PI must:

- Provide the IRB with a description of the device, reports of prior investigations with the device, the proposed investigational plan, a description of patient selection criteria and monitoring procedures, as well as any other information deemed necessary by the IRB.
- Provide the IRB with the assessment made by the FDA.
- Provide the IRB with a risk assessment and rationale used in making its risk determination [21 CFR 812.150(b)(10)].
- Obtain an IDE from the FDA by providing technical characteristics of the device, the initial risk assessment, results of any prior studies (laboratory, animal and human involving the device) and the complete proposal and consent form to the FDA.
- Provide the IRB with an explanation of its determination and any other information that might assist the IRB in evaluating the risk of the study if the PI acting as sponsor determines that the device is of non-significant risk.
- Report all changes to be made in the eligibility criteria or study design during the course of the research to the HIC via a full board amendment prior to initiating the changes.
- Report all adverse reactions and unexpected events directly to the FDA within 10 working days of occurrence [21 CFR 812.46(b)] and the IRB according to the HIC SOP "Identifying, Reporting, and Reviewing Adverse Reactions and Unexpected Events".

An IDE is not required for off-label use of an FDA-approved device used by a physician in the practice of **clinical care**. However, the results of an off-label use of a medical device cannot be presented or published as research.

An IDE is not required when the IRB determines the study involves the use of a non-significant risk device or devices that are substantially equivalent to currently marketed devices.

The FDA may assume jurisdiction over a study testing a non-significant risk device at any time, if warranted.

*Please see FDA Center for Devices and Radiologic Health web site at www.fda.gov for examples of Non Significant Risk (NSR) and Significant Risk (SR) devices and the informed consent and IRB regulations.

IDE Exempt Studies

The following are instances in which studies are exempt from having an IDE:

- Studies that are conducted with legally marketed devices used according to labeling do not require an IDE.
- Studies that use in vitro diagnostics labeled “for research purpose only” as per 21 CFR 809.10(c) and if the testing is:
 - Non-invasive,
 - Does not require an invasive sampling procedure that presents a significant risk,
 - Does not introduce energy into a subject, and
 - Is not used as a diagnostic procedure without confirmation by another medically established diagnostic product or procedure

Study Costs under an IDE

Federal regulations allow sponsors to charge for an investigational device; however, the charge should not exceed the amount needed to recover the costs of manufacture, research, development and handling of the device [21 CFR 812.7(b)]. A sponsor must state the amount to be charged, justify the amount and verify that it does not constitute commercialization [21 CFR 812.20(b)(8)]. The FDA generally allows sponsors to charge PIs who may pass the charge on to the participants.

The PI is required to clearly include the amount charged to the participant in the informed consent documents.

Submission Requirements for Device Studies

Significant Risk (SR) Studies –The following documentation must be submitted in order for the HIC/IRB to review SR device studies:

- A newly assigned IDE Number or a letter from the FDA stating that an IDE is not required. Documentation must be included (letter from FDA or contract) that verifies that the IDE is current. The IRB will not issue final approval until the current IDE number is provided to the HIC. However, the research can be reviewed by the IRB prior to or during the application process. 21 CFR 312.2(b).
- Submission of the Medical-Behavioral Protocol Summary Form (PSF) with Appendix F and all other documents listed in the directions of the PSF.
- Submission of other documents that specify device costs, the full protocol, instructions of device use, appropriate labeling, and a detailed device accountability plan. (e.g. receiving, disposal, storage, dispensing, record keeping, final disposition after the study is completed or has been terminated).

- For radiation-emitting devices a clearance by the Radiation Safety Committee should be submitted with the protocol.

Non-Significant Risk (NSR) Studies – The following documentation must be submitted for review of NSR studies by the HIC/IRB:

- Sufficient documentation to justify that the device and/or its proposed use does not pose a significant risk to participants (complete protocol with scientific justification and, device use and description, appropriate labeling, device cost, and a detailed device accountability plan). [21 CFR 812.2(c)].
- Submission of the Medical-Behavioral Protocol Summary Form (PSF), with Appendix F and all other required documents listed in the PSF. (e.g. receiving disposal, storage, dispensing, record keeping, final disposition)

*Note: Although an IDE is not required for NSR studies the IRB may request that one be provided (see IRB Review of Device Studies below).

IRB Review of Device Studies

The IRB at WSU must do their own risk assessments for all devices used in a protocol enrolling human participants in research regardless of whether a device has been given non-significant risk or significant risk status by the FDA.

An appropriate member of the IRB committee, or a consultant who is knowledgeable about the control of medical devices, will review and approve the investigator's plan as a condition of approval of the research.

If there are additional concerns in determining if a SR or NSR device study can be approved, the IRB may, request that:

- The PI submit other support documents which describe any prior studies using the device, an investigational plan, a description of how participants are selected, and data and participant safety monitoring procedures.
- A risk assessment be conducted by the sponsor (or PI, in the case of a PI-initiated study) that includes the rationale used in making the risk determination.

The FDA has provided a list of both NSR devices and SR devices in the IRB Information Sheets-Medical Devices that may serve as guides for the IRB in determining the appropriate action during the review of protocols involving a device. The lists of NSR and SR devices are available for reviewers to access on the HIC Website and at each convened meeting of the IRB.

In determining if a SR or NSR device study can be approved, the IRB will compare the anticipated risks and benefits of the experimental device and the risks and benefits of alternative devices or procedures.

If an IRB disagrees with the initial risk assessment provided by the PI and/or sponsor, the IRB may request that an IDE application be submitted to the FDA or that a letter from the FDA be provided to the IRB indicating that an IDE would not be required.

If an IRB determines that an investigator has submitted for approval a study involving a NSR device when the device is determined to be an SR device then the IRB is required to notify the investigator, and where appropriate, the sponsor. [21 CFR 812.66]

NSR Review

The determination of non-significant risk status is *independent* of the determination by the IRB as to whether or not the research protocol is eligible for expedited review. (45 CFR 46.110, 21 CFR 56.110, VHA Handbook 1200.5 15(b)). Some NSR studies may qualify as minimal risk [21 CFR 56.102(i)].

When the IRB determines that the study device is of NSR in a particular research protocol, no IDE or letter from the FDA is required and the IRB can proceed to review the study criteria (risks minimized, acceptable risk/benefit ratio, equitable selection of participants, proper informed consent, safety monitoring, protection of privacy and confidentiality and special protections of vulnerable participants). [21 CFR 56.111, VHA Handbook 1200.5 15]

If the study is approved by the IRB, the PI must comply with the abbreviated IDE requirements found at 21 CFR 812.2(b) and VHA Handbook 1200.5 15.i].

SR Review

Full board review will be required for all significant risk device studies because they are considered to be more than minimal risk.

When the IRB determines that the use of the device in a particular protocol may be of SR, the IRB will require the PI and/or sponsor to: (a) provide an IDE number or (b) provide a letter from the FDA indicating that an IDE is not required. The IDE number or letter indicating that an IDE is not required must be provided to the IRB before approval may be granted.

In addition to requiring an IDE for SR studies, the IRB will review the protocol according to the following: minimization of risk, acceptable risk/benefit ratio, equitable selection of participants, proper informed consent, safety monitoring, protection of privacy and confidentiality and special protections for vulnerable participants.[21 CFR 56.111]

Informed Consent Forms

All medical device studies involving human subjects require informed consent. The HIC provides an informed consent template with all of the necessary key elements. The specific key elements for device studies are as follows:

- A clear statement that the device is investigational and has not been approved by the FDA for clinical use or, if applicable, that the device has been approved for specific clinical uses but not for the use being studied,

- A brief lay description of the device and what it is designed to do,
- Must not describe the issuance of an IDE as an approval or endorsement by the FDA,
- Must state in the confidentiality section that the FDA may review the research and the subject's medical records to verify study data,
- Must include a list of the various alternatives to participation in the study including the name of standard therapies available with approved devices as well as other experimental treatments with investigational devices,
- Must provide specific information regarding cost to the participant, such as whether or not the sponsor is supplying the device at no charge, whether the subject or their insurance carrier will be billed for the device or that the cost may not be covered by insurance because the therapy is experimental, and
- A discussion of the cost of implanting and, if anticipated as part of the study, the cost of removing the device.

Documentation

The Initial Submission Review Form is used by each reviewer to document whether or not the risk of the device is non-significant or significant. If the IRB has determined that the use of the device is a NSR study, the reviewer documents:

- That the device is not an implant,
- The device is not used to support or sustain human life,
- The device is not of significant importance in diagnosing, curing, mitigating or treating disease, or otherwise preventing impairment of human health, or
- Does not present a potential for serious risk to the health, safety, or welfare of a participant.

If the IRB has determined that the use of the device is a SR study, the reviewer will document:

- Whether or not the PI has obtained an IDE from the FDA, or
- Whether the PI has submitted an IDE application to the FDA or obtained a letter from the FDA indicating that an IDE would not be required.

Whenever a protocol involving research on an unapproved medical device is reviewed by an IRB, the decisions concerning the determination of non-significant or significant risk must be documented in the IRB Committee minutes with clearly stated examples from the protocol that justify the decision.

Expanded/Treatment Use of Investigational Devices

The FDA recognizes the term "compassionate use" for investigational devices. **Compassionate use** may occur when a device that is being tested in a clinical trial is the only option available for a patient with a serious condition but who does not qualify for the trial. Such uses require that the sponsor obtain prior FDA approval of a protocol deviation under 21 CFR 812.35(a). Prior approval for compassionate use must be obtained before the device is used. The criteria for compassionate use for a single patient or small group access to an investigational device are:

- A serious disease or condition

- No available alternative treatments

To apply for FDA approval, the PI must provide information to the FDA regarding the patient's condition, a discussion why alternative therapies are not satisfactory and why the risk of using the investigational device is no greater than the risk from the disease or condition; an identification of any deviations in the approved clinical protocol that may be needed in order to treat the patient, and the patient protection measures.

There are occasions when compassionate use may occur even if there is not an IDE for the device. In this situation the physician would submit the compassionate use request directly to the FDA

When a physician wishes to use an investigational device for treatment purposes in a non-emergent situation and the patients meet the criteria set forth in the FDA regulations for a treatment IDE, a prospective research protocol must be submitted to the IRB for review and approval and an informed consent must be obtained prior to the use of the device.

When an investigational device is required for emergency situations to save a patient's life, prospective IRB review and approval would not be required and this type of situation would be covered by the HIC Policy/Procedure: "Emergency Single Time Use of a Test Article".

Compassionate Use does not apply to drugs. Please see (Policy/Procedure "Compassionate and Expanded Use of Drugs and Devices") for additional information.