Guidance on Use of Investigational Medical Devices in Human Subjects Research

1) What is a Medical Device?

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
- intended to affect the structure or any function of the body of man,
  AND which does not achieve its primary intended purposes through chemical action within or on the body of man and which is not dependent upon being metabolized for the achievement of its primary intended purposes (21 U.S.C. 321(h)).

2) What is an Investigation?

A clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device.

3) What is an Investigational Medical Device?

An investigational device means a device, including a transitional device that is the object of an investigation.

Simply using a device as part of a study does not make the device investigational. For example, if a non-invasive, unapproved device is used to make measurements as part of a study, but the study is not about the device, then the device is not an investigational device for the purposes of that study. For example, if an investigator wishes to use an unapproved device to measure cerebral blood flow but the study is not about the device (not assessing the safety or effectiveness of the device), then for that study, the unapproved device would not be investigational. Whereas the device would be an investigational device when used in a study designed to assess the feasibility and safety of making cerebral blood flow measurements during cardiac surgery.

Use HRP-307 WORKSHEET Devices in order to help decide whether an investigational device requires an IDE, qualifies for an abbreviated IDE or is IDE exempt

4) When do the FDA regulations apply?
FDA regulations apply when a study evaluates the safety or effectiveness of a medical device in subjects, healthy control subjects, or human specimens. FDA Informed Consent and IRB (21 CFR 50, 56) regulations apply as well.

5) When do the FDA regulations not apply?
FDA regulations would generally not apply to studies:
• using an FDA approved device to test a physiologic principle where no data is collected about the device;
• using an FDA approved device to address a research question and no data is collected about the device; or
• using an FDA approved device for clinical purposes (e.g., monitor a side effect, measure treatment progress as long as there is no intent to collect safety or effectiveness data or develop the device for marketing.
An example would be use of an MRI to measure a clinical outcome in a study that has nothing to do with the MRI itself.
However, if the device used for one of these purposes is homemade by the investigator, (e.g., a lever designed to raise the arm to measure flexibility), the informed consent should state that the device is **not approved by the FDA**.

6) What is an Investigational Device Exemption (IDE) and when is it required?
An IDE allows the investigational device to be used in a clinical study in order to collect safety and efficacy data required to support a marketing application. The term "exemption" in this case means exempt from laws prohibiting unapproved products to move in interstate commerce.

FDA Investigational Device Exemptions (IDE) (21 CFR 812) regulations may apply for studies designed to:
• support marketing applications;
• collect safety and effectiveness information (e.g. for a new intended use of a legally marketed device);
and
• Studies of an unapproved device or a new intended use of an approved device, even if no marketing application is planned.

7) What are the three regulatory categories for device studies described in the IDE regulations (21 CFR 812)?
Research that involves assessing the safety or effectiveness of a medical device must fit in ONE of the following categories:
1. Studies exempt from IDE requirements;
2. Significant Risk (SR)-device research with formal IDE submission to FDA;
3. Non-Significant Risk (NSR) device research, which with IRB approval is considered to have an approved IDE; referred to as an Abbreviated IDE.

8) Who decides whether a device study is SR or NSR?
Sponsors are responsible for making the initial risk determination and presenting it to the IRB. Unless FDA has already made a risk determination for the study, the IRB must review the sponsor's SR or NSR determination for every investigational medical device study reviewed and modify the determination if the IRB disagrees with the sponsor. If the IRB disagrees with the Sponsor's NSR determination, the PI may be asked to contact the FDA to obtain an IDE.

If FDA has already made the SR or NSR determination for the study, the agency's determination is final.

Use HRP-418 – CHECKLIST Non-Significant Risk Device to determine if the device study is SR or NSR.

9) What are the IRB's responsibilities when it receives a device study for IRB review?
• If the device, as used in study, is NOT exempt and study does NOT have a valid IDE or FDA correspondence stating device is NSR, then IRB makes the SR or NSR determination **based on the proposed use of the device in the study**. The SR/NSR determination is made by the **full IRB at a convened meeting** using information such as the sponsor's risk designation and justification criteria, a description of the device, reports of prior investigations, proposed investigational plan, and subject selection criteria. The sponsor should provide the IRB with a risk assessment and the rationale used in making its SR or NSR determination.
• An IRB may agree or disagree with the sponsor's initial NSR assessment.
• If the IRB determines the study is NSR, the IRB may approve the study using the criteria at 21 CFR 56.111. The study may begin without submission of an IDE application to FDA.
• If the IRB disagrees with the sponsor's NSR assessment and decides the study is SR, the IRB must tell the clinical investigator, and where appropriate, the sponsor. (See 21 CFR 812.66)
• An IRB may approve the study as an SR device study, but the study may not begin until

FDA approves the sponsor's IDE application.
• To facilitate the IRB's review of the study, an IRB may ask the sponsor for proof (i.e., a copy of FDA's approval or conditional approval letter) that an SR study has an FDA-approved IDE application.
• The IRB should document its SR/NSR determination in the IRB meeting minutes.

10) What should the IRB's consider when making the SR and NSR determination?
The risk determination is based on the proposed use of a device in an investigation, and not on the device alone.

SR studies are those that present a potential for serious risk to the health, safety, or welfare of a subject.

IRBs should consider the potential harm the procedure could cause as well as the potential harm caused by the device.

11) What is meant by IDE Exempt?
Certain device studies are "Exempt" from the IDE requirements. Exempted investigations include investigations involving one of the following:

1. The most common IDE exempt studies are those involving a marketed medical device in which the device is used or investigated in accordance with the indications in the cleared labeling. For these studies the investigator should provide, and the IRB should review, label information in order to compare the intended use in the protocol with the approved indications. Device approval indications may also be found by searching one of the FDA Device Approvals and Clearances databases.

2. Other examples of studies exempt from IDE requirements are consumer preference testing, testing of a device modification or testing of a combination of two or more devices in commercial distribution if the testing does NOT collect safety or effectiveness data, or put subjects at additional risk.

3. In addition, diagnostic device studies [**e.g., in-vitro diagnostic reagents and test kits such as pregnancy test kits, and imaging systems such as magnetic resonance imaging (MRI)**] are exempt from the requirements under certain circumstances. The study is exempt as long as the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling, and if the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or

procedure. [21 CFR 812.2(c)(3)].

12) Does device classification (Class I, II, III) factor into IRB determinations?
A sponsor's detailed protocol may list a device as Class I, II or III. FDA classifies devices based on the level of control necessary to assure safety and effectiveness of the device for marketing (**not research**). Controls range from general requirements such as labeling, not misbranding, and good manufacturing practices to special controls such as specific instructions for use or post marketing surveillance requirements.

The classification is risk based so is indicative of the type of submission required for FDA to clear a device for marketing. Class II and Class III devices require the type of marketing route that most often involves clinical trials. Therefore, these are the types of devices seen in research for which the IRB is involved in the regulatory determinations addressed in the questions above.

13) Which regulatory device categories may be eligible for Expedited IRB review?
For a device study to be eligible for Expedited Review under Expedited Category 1, **the device must present no more than minimal risk to the subject, and meet one of the criteria in Category 1b:**

Expedited Category 1b- Research on medical devices for which
(i) an IDE application (21 CFR Part 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**.

**Example: Study presents documentation from FDA indicating that an IDE application is not required or study meets all criteria to be IDE exempt in vitro diagnostic device21 CFR 812.2(c)(3).*
*** An approved Device used in research according to its approved labeling is considered Exempt from IDE requirements- 21 CFR 812.2(c)(1 or 2).*

***Note:** Expedited Category 1 should not be used for studies that involve use of a device only, (no testing or data collected on or about the device), as FDA regulations do not apply. Expedited Category 4 may be considered for studies that **use, but not test**, a device.*

14) What if I am using a Mobile Application in my research study?
The FDA mobile medical device regulations apply if you are using a mobile application in a research study, and that is being used to facilitate the diagnosis, or mitigation, of a disease, or affect the function or structure of the human body.

Please use the Guidance for Research Involving Mobile Apps or Mobile Medical Apps and refer to HRP-336 WORKSHEET Mobile Apps and Mobile Medical Apps if the study uses Mobile Apps.

15) What is a Humanitarian Use Device?
A HUD is a medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

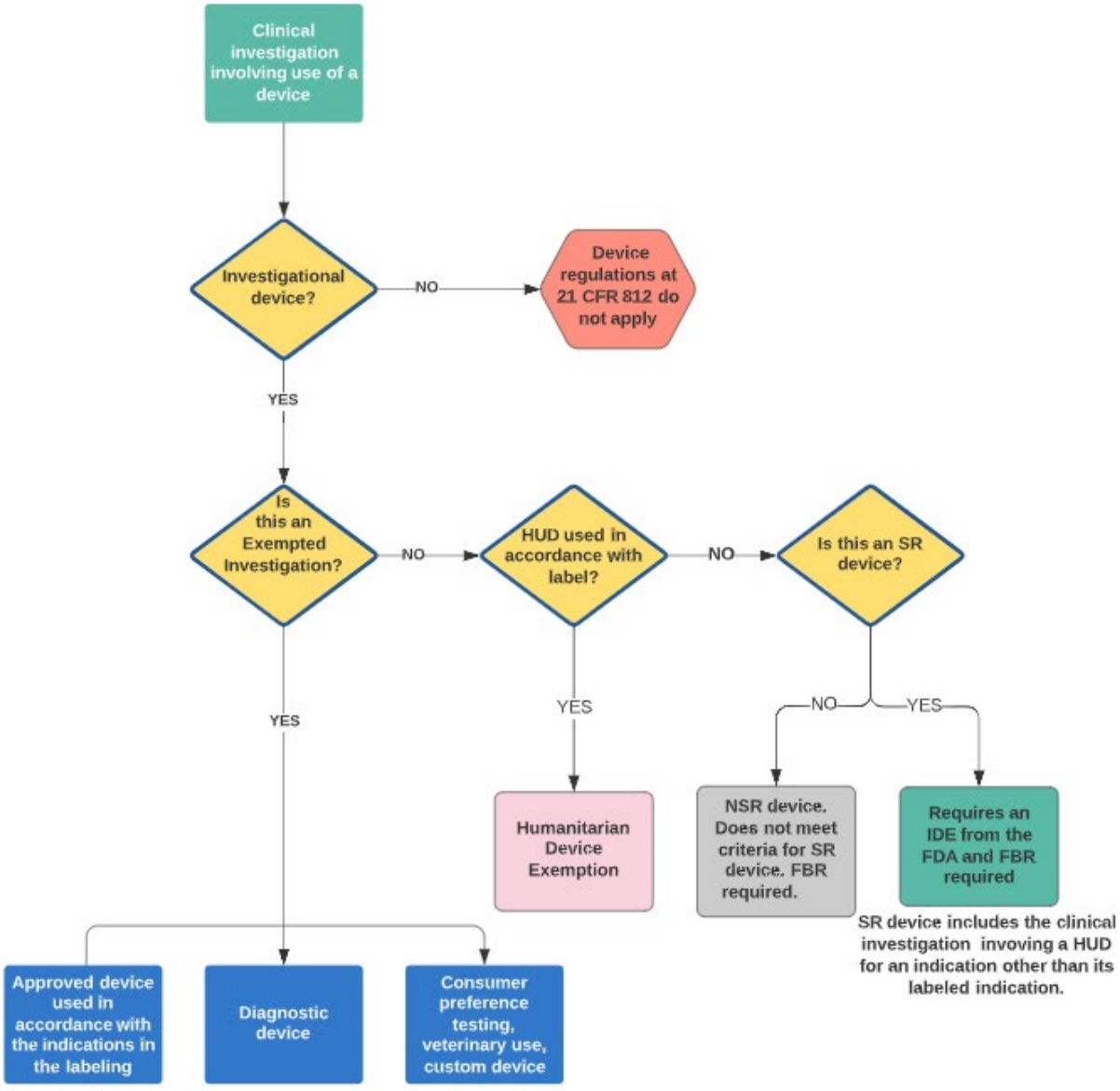
Use of a HUD in medical practice, within its approved labeling does not constitute research. Initial IRB approval of a HUD should be performed at a convened IRB meeting.

Humanitarian Device Exemption (HDE) holder may collect safety and effectiveness data in a clinical investigation for the HDE-approved indication(s) without an IDE.

Clinical investigation of HUD for different indication must be conducted in compliance with IDE regulations.

Use HRP-323 WORKSHEET Criteria for Approval for HUD

Use the Device decision tree below:



Other helpful Links and Resources:

Frequently Asked Questions About Medical Devices - FDA
Significant Risk and Nonsignificant Risk Medical Device ... - FDA
FAQ's about Investigational Device Exemption-FDA
Guidance for Industry and FDA Staff - In Vitro Diagnostic (IVD)-FAQ's
Examples of Mobile Apps that are not Medical Devices.
IRB Oversight of Humanitarian Use Devices - FDA
General Wellness: Policy for Low Risk Devices | FDA
Software as a Medical Device (SaMD) | FDA