University of South Alabama
Humanitarian Use Devices (HUD): Guidance for Physician/Investigators

For further detail, see IRB SOP 1004: Humanitarian Use Device

Background:

Humanitarian Use Devices (HUDs) are a special class of device that is marketed under the Humanitarian Device Exemption (HDE) approval process by the FDA. HUDs are intended to benefit patients in the treatment or diagnosis of a disease or condition that affects fewer than 8,000 individuals in the United States per year. HUDs are given a special class of FDA approval because they have not been clearly demonstrated to be effective; rather, they have been shown to be safe and probably effective for their intended condition. With this limited approval, the FDA requires IRB review and approval at full board before these devices can be used to treat patients.

SECTION I: Definitions

Emergency Use: the use of an investigational drug or biological product with a human subject in a life-threatening situation in which no standard acceptable treatment is available and in which there is not sufficient time to obtain IRB approval

Compassionate Use: also called 'Expanded Access', a potential pathway for a patient with an immediately life-threatening condition or serious disease or condition to gain access to an investigational medical product (drug, biologic, or medical device) for treatment outside of clinical trials when no comparable or satisfactory alternative therapy options are available

Humanitarian Use Device (HUD): A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year (FDA 21 CFR 814.3(n)).

Humanitarian Device Exemption (HDE): An HDE application is a marketing application that is similar to a premarket approval (PMA) application in that the applicant must demonstrate a reasonable assurance of safety, but in an HDE application, the applicant seeks an exemption from the PMA requirement of demonstrating a reasonable assurance of effectiveness. A device that has received HUD designation is eligible for HDE approval if, among other criteria, the device will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from use of the device outweighs the risk of injury or illness from its use, taking into accountthe probable risks and benefits of currently available devices and alternative forms of treatment.

Non-significant Risk (NSR): A non-significant risk (NSR) device is one that does not meet the definition of a significant risk device.

Off-Label: when a FDA approved device or drug is used for a purpose that is not approved by the Food and Drug Administration.

Significant Risk Device (SR): device study involves an investigational device that either-

- is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a research subject;
- Is meant to be used to support or sustain human life and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Plays an important role in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject;
- Otherwise presents a potential for serious risk to the health safety or welfare of a subject

SECTION II: Types of HUDs

1. ***Use in Clinical Practice- Non-Research***

A HUD is considered non-research if the device is used in accordance with the FDA approved indication *and* safety and/or effectiveness data is *not* collected.

- The HUD may only be used after IRB approval has been obtained for the use of the device for the FDA approved indication or off-label.
- HUD use is subject to continuing review by the IRB.
- An IRB approved consent is not required. Routine procedures must be followed to obtain the usual consent to treat necessary for clinical care according to all related standard of care practices.

2. ***Use in Investigational Research***

A HUD is used in investigation research if the device is being used off-label or is being used on-label and collecting safety and/or efficacy data.

The use of a HUD requires prior IRB approval. For research under a HDE, the scope of the IRB approval is to confirm the planned use is consistent with the FDA approved indication for the HDE.

Researchers who study a HUD for a new indication must submit an IDE application to the FDA if the device is a significant risk device. The investigational use of a HUD under these conditions is a clinical investigation and must be conducted in compliance with 21 CFR parts 812, 50, 54 and 56.

3. ***Emergency Use***

If a physician in an emergency situation determines that IRB approval for use of the HUD cannot be obtained in time to prevent serious harm or death to a patient, the HUD may be used without prior IRB approval. In this situation, the HDE holder may ship the HUD, based on the physician's certification of the emergent need.

The following conditions must be present for emergency use:

- Patient's life is threatened and patient needs immediate care. The term "life-threatening" is meant to include the presence of serious disease or condition that involves risk of irreversible morbidity, such as loss of eyesight.
- No generally accepted alternative exists.
- There is no time to obtain FDA approval.

If possible, the physician should take as many of the following actions as possible prior to using the HUD:

- Independent assessment of an uninvolved physician.
- Contact the IRB to obtain concurrence for use of the HUD. Notification to the IRB Office should include identification of the patient involved, date of the use and reason for the use.
- Authorization from the IDE sponsor, if an IDE exists for the device.
- Obtain treatment informed consent for the patient or his/her legally authorized representative and explain to the patient or parent that the HUD is being used for an indication outside the approved labeling
- Provide the patient with the device information packet and an information sheet explaining the FDA's HDE program.
- Develop a schedule to monitor the patient

After use of the device, the following actions should be taken:

- No later than 5 business days send a report to the IRB through IRBnet describing the use, reason for the use, and describing patient's current status and protection measures that were followed.
- Provide the IRB with an follow-up report and notify the HDE holder of the use and describe patient's current condition within 30 days.
- Monitor the patient according to the identified schedule and report any issues in the use of the device (reportable events, unanticipated problems, etc.) to the HDE holder and the IRB, as appropriate

4. Compassionate Use

Compassionate use of an HUD is the "off-label" use of an HUD, or using the HUD for other diagnosis or condition from which it is intended. If a physician determines there is no emergency, but that there is no alternative to the HUD for the patient's condition and the physician notifies the IRB of the use BEFORE it occurs and obtains IRB approval for the use. Before using the HUD, the physician using the HUD should take the following actions:

- The physician must contact the HDE holder to determine any restrictions and report the outcome of the compassionate use, including any safety related information to the HDE holder or the FDA
- Provide the HDE holder and IRB with a brief overview of the planned use of the device, identify the patient, why use of the device is necessary the plan for monitoring the patient and obtain full board IRB approval prior to use of the device
- Obtain treatment informed consent for the patient or his/her legally authorized representative and explain to the patient or parent that the HUD is being used for an indication outside the approved labeling
- Provide the patient with the device information packet and an information sheet explaining the FDA's HDE program or include this information in the consent process
- Develop a schedule to monitor the patient

The above only refers to compassionate use for *devices*. Please refer to IRB SOP 1003: Compassionate/Treatment Use for information on compassionate use in drugs.

The emergency use of a HUD must be followed according to ***IRB SOP 1002: Emergency Use: Investigational Drugs, Biologics and Device***

After emergency use occurs, the physician must submit a follow-up report on the patient's condition and information regarding the patient protection measures to the USA IRB and to the manufacturer within five (5) working days. The reporting criteria is listed in IRB SOP 1002 noted above.

SECTION III: USA IRB HUD Application Requirements

The HUD user or designee must complete and submit the following documents:

- IRB Application
- Clinical informed consent or informed consent document from HDE holder
- Letter from FDA to the HDE holder (indicates that an application for the HUD has been reviewed and approved by the FDA)
- Device Operator's Manual, if applicable
- HUD brochure / patient labeling or other consumer information, if applicable
- HUD training certificate (see Section IV below)

It is a federal requirement to provide all HUD patients with the labeling and patient materials (such as patient information brochure) prepared by the HDE holder prior to the patient receiving the whenever feasible.

Section IV: HUD Training Requirements

The Investigator must ensure that physician/investigators possess the credentials necessary to use the device, are knowledgeable regarding the use of the device and abide by terms of the USA IRB approval letter.

FDA Training Requirements:

- In the event the FDA requires training, the HUD user and all other health care providers that may potentially use the HUD device at USA must receive training by the HDE holder.
- The FDA approval orders of HDEs are available for review on their website, at (just select the HDE number): http://www.fda.gov/MedicalDevices/ProductsandMedicalProcedures/DeviceApprovalsandClearances/HDEApprovals/ucm161827.htm#2

SECTION V: IRB Review

IRB review is required for several reasons, all related to patient safety. The statue and the regulations require initial review by a convened IRB. However, there is an exception to this rule for emergency situations in which the physician determines that approval cannot be obtained in time to previous serious harm or death to the patient. With respect to HUD review, the IRB will consider the ethical

impact related to the use of the device and patient safety. The HUD IRB Application form must be submitted via IRBNet for review by the convened IRB.

The HDE holder must have both HUD designation and approved HDE from FDA before device is shipped to institutions with IRB oversight, except as noted above in Emergency Use situations.

Decision Tree for IRB when Reviewing Applications for HUD Use

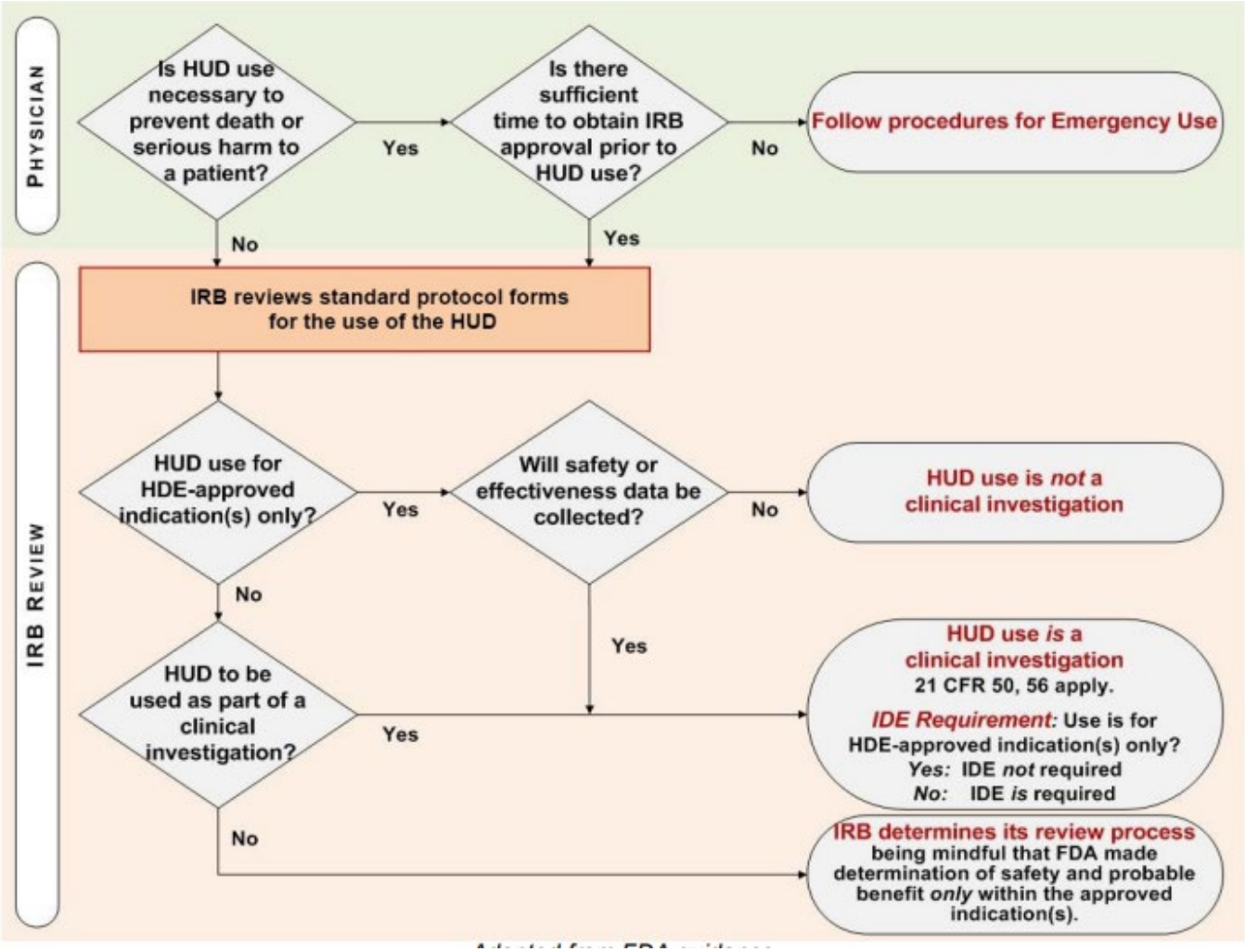

Photo Source 1: MD Anderson Cancer Center, Humanitarian Use Device Policy https://www.mdanderson.org/content/dam/mdanderson/documents/Research-Centers-&-Institutes/office-of-clinical-research-administration/hrpp-manual/guidance/Humanitarian_Use_Device.pdf

SECTION VI: Physician Responsibilities

- The physician using the HUD is responsible for providing all applicable information regarding the use of the HUD to the IRB and obtaining IRB approval before the device is used.
- Ensure that a Humanitarian Device Exemption (HDE) exists for use of the HUD and that the proposed use meets the HDE requirements.
- Submit a basic written plan for use of the HUD, HUD manufacturer's product labeling, clinical

brochure and/or other pertinent manufacturer information materials, the FDA HDE approval letter, and obtain IRB approval prior to use.
- Submit documentation to the IRB for continuing review of the HUD.
- Submit adverse events. This reporting is in addition to FDA and/or manufacturer reporting requirements in accordance with 21 CFR 803.30.
- Obtain consent for Research HUDs or where the IRB has required consent for clinical use of an HUD.

- Report any serious adverse event related to the use of the HUD on your patient to the USA IRB within 5 working days.
- Report any information regarding changes in labeling and potential patient risk received from the manufacturer to the USA IRB

The specific requirements for reporting are set forth in the Medical Device Reporting Regulation, at 21 CFR Part 803.

SECTION VII: IRB Responsibilities

- Provide full board initial review of use of the HUD. The IRB may approve use of the HUD without any further restrictions, or under a protocol, or on a case-by-case basis. The convened Board may make the determination at initial review that continuing review may occur using the expedited procedure if the HUD is not being used in the course of a research study.
- Provide continuing review at the full board or by expedited review at least annually.
- The IRB must ensure that the proposed use is within the FDA-approved indication and that the use of the device does not exceed the scope of the FDA's approval.
- The IRB will verify that the device does not pose an unreasonable risk of illness or injury to the recipient, and that the probably benefit outweighs the risks from use of the device.
- The IRB does not have to review and approve each individual use of the HUD. The IRB may approve the use of the device in general, for groups of patients clinically appropriate for the device's intended use.
- The IRB may consider the provider's qualifications through training and expertise with use of the device. The IRB may place limitations on the use of the device based upon: one or more measures of disease progression; prior use of and failure of the alternative treatments; reporting requirements to the IRB; appropriate follow-up precautions and evaluations; or any other criteria IRB determines to be appropriate.
- The IRB may require re-review at an interval of time more frequent than annually, or may want to conduct re-review after a specified number of patients have been accrued.

SECTION VIII: Frequently Asked Questions

Is use of a HUD according to the manufacturer's instructions and labeling considered research?

No, use by a physician of a HUD for the purpose for which it is marketed is not research. However, use of a HUD in accordance with its label (on label) is permitted in the course of medical care only after the use or "protocol" has been submitted to and authorized by the IRB.

Who is responsible for ensuring that a HUD is not administered to or implanted in a patient prior to obtaining IRB approval at a health care facility?

The physician/investigator is responsible for obtaining IRB approval before the HUD is administered to or implanted in a patient. The manufacturer who is usually the Humanitarian Device Exemption (HDE) holder is responsible for ensuring that the HUD is only used in facilities having an IRB constituted and acting in accordance with CFR 21 Part 56. The HDE holder will also not ship the device to an institution or physician/investigator if they are not in possession of IRB approval. Records of the names and addresses of the facilities to which the HUD has been shipped, correspondence with reviewing IRBs, as well as any other information required by a reviewing IRB or FDA must be maintained by the HDE holder and sent to FDA.

How do the regulations affect the use of the HUD in my practice?

There are 3 scenarios that are governed by FDA regulations in which a HUD may be used; 1.) the indication (on label) it was approved for, 2.) off-label, emergency use, and 3.) off-label, non-emergency use. The regulations affect the documentation and approvals that are required for each scenario.

Do I have to submit each individual "on label" use of a humanitarian use device (HUD) to the IRB for approval before use?

No. The IRB does not review and approve each individual use of a HUD. As long as the use of the HUD is within the FDA approved indication, the IRB approval to use the device is sufficient. The IRB requires that each on label use of an HUD must be reported to the IRB office within 5 working days. The summary should include the date, indication for use, any adverse effects, patient outcome and any additional information stipulated in the original IRB approval.

In an emergency situation, can a HUD be used "off label" (i.e., outside of its approved indications for use)?

Yes. The FDA does permit a HUD to be used off label in an emergency situation, but they require that certain patient protection measures be followed before the use occurs. Because IRB review and approval is required before a HUD is used within its approved labeling, a HUD should not be used outside of its approved labeling without similar restrictions. That is, in an emergency situation, a HUD may be used off-label to save the life or protect the physical well-being of a patient, but the physician/investigator and manufacturer (the HDE holder) should follow the emergency use procedures governing such use of unapproved devices as described in the IRB Policy; IRB 12, Emergency Use of a Test Article (Compassionate/Humanitarian Use) According to this policy, before the device is used, if possible, the physician should obtain the IRB chairperson's concurrence, informed consent from the patient or his/her legal representative, and an independent assessment by an uninvolved physician. In addition, authorization from the manufacturer would be needed before the emergency use of the HUD. After the emergency use occurs, the physician should submit a follow-up report on the patient's condition and information regarding the patient protection measures to the IRB and to the manufacturer within 5 working days. The manufacturer then has a requirement to submit this report to the FDA as an amendment to the HDE.

What if the situation is not an emergency, but the physician determines that there is no other alternative device for the patient's condition? Can a HUD be used under this type of situation (i.e., compassionate use)?

Yes, a HUD may be used for compassionate use. This is the third type of "use" as described above, i.e., off label, non-emergent. In addition to addressing the patient protection measures, prior FDA approval of the HUD for compassionate use is required just as it is for compassionate use of any unapproved device. According to the FDA's policy on compassionate use, a physician who wishes to use a device for compassionate use should provide the HDE holder (manufacturer) with a description of the patient's condition and the circumstances necessitating treatment with the device, a discussion of why alternative therapies are unsatisfactory, and information to address the patient protection measures. For compassionate use of a HUD, the physician should provide this information to the manufacturer, who would then submit a HDE amendment for FDA approval before the use occurs. FDA will review the information in an expeditious manner and issue its decision to the HDE holder. If the request is approved by FDA, the physician should devise an appropriate schedule for monitoring the patient, taking into consideration the limited information available regarding the potential risks and benefits of the device and the specific needs of the patient. The physician must submit a request to the IRB for the compassionate (off label) use of the device with the manufacture's authorization, FDA authorization, and a written description for monitoring the patient following use. The IRB will expedite this request. The physician may not use the device until he as received concurrence from the IRB. 3 The physician must submit a report to the manufacturer and the IRB following use of the device reporting on the patient's outcome and progress.

Who determines if a device is Significant Risk or Non-Significant Risk?

The manufacturer will determine is the device is significant risk or non-significant risk. However, the IRB has the authority to increase the risk level.

Is informed consent required when treating/diagnosing a patient with a HUD?

Yes. Informing the patient is always required prior to initiating any treatment. However, the type of consent varies. In short, if the HUD is not research, then the clinician can use the standard-of-care, treatment consent. If the HUD is research than an informed consent, with all federal requirements, is needed. Refer to the flowchart in this document to assist you on determining when an informed consent is needed.

What if the Manufacturer asks me to collect and provide them safety and effectiveness data to support a PMA? Is an IDE needed? Is IRB approval and informed consent required?

This question really has several parts. If the manufacturer wants to collect safety and effectiveness data to support a PMA under their approved HDE, the health care provider can supply that information. But, if the HUD is the subject of a clinical investigation, (one in which safety and effectiveness data is being collected to support a Pre-Marketing Approval application), IRB approval and informed consent are required. (21 CFR Parts 56 and 50) Here, you should talk to the staff at the IRB office to insure that what the manufacturer is asking you to provide is in compliance with the FDA regulations.

If the HUD is marketed and approved by the FDA and its use is not research, why is the IRB involved?

The IRB is involved for several reasons, all related to patient safety. The statute and the implementing regulation (see 21 CFR 814.124(a)) require IRB review and approval before a HUD is used. (There is an exception to this rule for emergency situations in which the physician determines that approval cannot be obtained in time to prevent serious harm or death to the patient.)

Resources:

21 CFR 914 (Subpart H) Humanitarian Use Devices
Humanitarian Device Exemption
HDE Approvals
21 CFR 803 Medical Device Reporting
USA IRB Standard Operating Procedures

Link to informational video on HUDs provided by the FDA (20 minutes):
http://fda.yorkcast.com/webcast/Viewer/?peid=679dff2747964a5c90c7274a7313255f