See Also CW HRPP SOP Manual

NOTE: This guidance only applies to use of a HUD in accordance with its approved labeling. Any use of a HUD that meets the definition of a clinical investigation must follow FDA federal regulations 21CFR parts 50 and 56.

What is a Humanitarian Use Device (HUD)?

A Humanitarian Use Device is a medical device, which falls under FDA regulations, intended to benefit patients in treatment or diagnosis of a disease or condition that affects, or is manifested in, not more than 8,000 individuals per year in the United States. The incidence limit was raised from 4 to 8 thousand with the passage of the 21st Century Cures Act. (21 CFR 814.3(n))

"A HUD is a legally marketed device, and its use within its approved indication does not constitute a clinical investigation. However, IRB or appropriate local committee approval is required before a HUD can be used at a facility for clinical care, with the exception of emergency use." (IRB Management and Function, Chapter 11-5)

HUD Pathway in the United States

In 1990, Congress established the HUD designation and HDE marketing pathway program. This program was created to encourage the development of devices for rare diseases or conditions. Congress recognized that the small market could create an economic disincentive for device development for rare diseases. Traditionally, in order for a device to enter the market in the U.S., there had to be a reasonable assurance that the device was safe and effective. Under the HUD/HDE pathway, the Sponsor is exempt from having to demonstrate device effectiveness, and needs to demonstrate that the device is safe and provides a probable benefit to the patient. Therefore, the HUD/HDE program is an alternative pathway for devices intended for rare diseases or conditions to enter the US market.

When used in an institution, regulations require a convened IRB to do the initial review of that HUD use, applying the same approval criteria as for any FDA regulated product, even though use of the HUD under the Humanitarian Use Exemption (HDE) is not considered research. This is primarily because use is based on safety and probable benefit but does not provide assurance of effectiveness. The device was not studied "normally" so there is very little actual data to support FDA's "approval." The FDA wants the IRB to be the gatekeeper until such time as the device can be approved by FDA via "normal" clinical trial pathways – meaning it no longer has a HUD designation. It is important for patients who are considering use of a HUD understand this distinction.

Humanitarian Device Exemption (HDE)

This indicates that the device is approved for marketing, but the approval is based on evidence of safety and probable benefit (rather than the "higher" standard of reasonable assurance of effectiveness. (21 CFR 814.2)

A HUD designation request is submitted to and approved by the Office of Orphan Products prior to the HDE submission. This is a review from the Office of Orphan Products that agrees that the patient population is less than the threshold of 8,000 patients per year.

Humanitarian Device Exemption or HDE is the marketing application for a HUD. These applications are exempt from the effectiveness requirement of the Safe Medical Devices Act the HUD designation should already be obtained prior to submission of the HDE

The HDE program has evolved over time and encourage the development of devices designed to treat or diagnose rare conditions. In 1990, the Safe Medical Devices Act included a provision to exempt qualifying devices from the requirement to demonstrate a reasonable assurance of effectiveness per Section 514 and 515 of the Food, Drug and Cosmetic Act.

The HDE should contain valid scientific evidence that demonstrates the safety and probable benefit of the device. Unique to HDE review is the standard of probable benefit as HDEs are exempt from the requirement to demonstrate effectiveness which is necessary for other marketing applications such as PMA premarket approval. The FDA reviewer's determination of whether the HDE demonstrates probable benefit includes many considerations. The FDA reviewer may accept a greater level of uncertainty in the data as a reasonable assurance of effectiveness is not required. The FDA reviewer may consider the intended use of the device including the target patient population and the size of the population. For example, the smaller the patient population, the greater the uncertainty FDA would expect. The reviewer may take into account currently available alternative treatments or diagnostics and may take into account patient perspectives on risk, uncertainty and probable benefit.

Information regarding comparable devices should also be provided. The applicant (to the FDA) should conduct a search within the device space and provide a statement that no other comparable device other than a HUD approved under HDE or a HUD for use under an approved clinical investigation is available to treat or diagnose the disease or condition. If the statement cannot be provided and there are alternative devices available, then HDE may not be an appropriate marketing pathway.

Once an HDE is approved, it is subject to several requirements unique to HDEs. **An IRB designated by the institution must provide oversight at medical facilities where HUDs are used. At CW the CW HRPP determines what IRB should serve as the IRB of record and also oversees the use in any CW facility.**

IRB Responsibilities:

FDA regulations 21 CFR 814 require IRB oversight of HUDs. Once the designated IRB has provided initial approval for the use of a HUD in an institution, it does not need to approve each individual use of that HUD. That said, the IRB or the institution may choose to limit the use based on certain factors as deemed appropriate. Any limitations or restrictions on the HUD use will be communicated to the physician requesting approval.

The IRB is required to:

- Follow the regulatory criteria for approval at 21 CFR 56.111 when reviewing use of a HUD.
- Use its discretion to determine how to approve use of a HUD, including consideration of professionals' qualifications through training and expertise to use the device.
- Consider the patient need for the HUD.
- Consider the likelihood that the device is appropriate for the patient's condition.
- Review the risks to the patients that are found in the product labeling.
- Conduct continuing review; when appropriate, the IRB may conduct the review accordance with the FDA regulatory criteria for an expedited review procedure unless risks are identified, or an IRB has policies for continuing review of a HUD that do not allow expedited review. This should be a substantive review of the risk/benefit information as well as any medical device reports (MDRs) and or sponsor's annual reports to the FDA.

The IRB may use its discretion to determine how to approve use of a HUD, including consideration of professionals' qualifications through training and expertise to use the device.

The IRB is not required to:

- Monitor the number of HUD uses per year (responsibility of HDE holder).
- Make a SR or NSR risk device determination when the device is used as approved by the FDA under the HDE for clinical care.
- Audit the medical records of patients who received the HUD; **however, the institution may conduct post approval quality monitoring of HUD use.**

- Function as HUD Data Monitoring committee.
- Apply the regulations at 45 CFR 46 (DHHS).
- Approve an informed consent; **however, local policy may require use of an IRB-approved consent document.**

Pediatric Considerations

For the purpose of a HUD request, the pediatric population is defined as those younger than 22 years of age. In general, the FDA will designate for the entire population, both pediatric and adult, if the population estimate of the disease or condition affects or is manifested in not more than 8,000 patients per year in the United States. If the overall population exceeds 8,000, a sponsor may pursue a pediatric population if that is less than 8,000.

Informed Consent

Informed consent is a requirement by policy at Children's Wisconsin.

Neither the FD&C Act nor FDA regulations require informed consent from patients who are treated or diagnosed with an HDE-approved HUD in the course of their clinical care. An IRB or appropriate local committee may, however, choose to require that patients receive certain information about the HUD when the committee approves use of the HUD for clinical care at a facility. If a committee requires that patients receive a written document prior to use of the HUD in clinical care, the document should include much of the information found in the HDE patient labeling. If no patient information packet is available, the HDE holder may consider including the following in any written information provided to patients: an explanation that the HUD is designed to diagnose or treat the disease or condition described in the HDE labeling and that no comparable device is available to treat the disease or condition; a description of any ancillary procedures associated with the use of the HUD; a description of the use of the HUD; all known risks or discomforts; and an explanation of the postulated mechanism of action of the HUD in relation to the disease or condition. The IRB or appropriate local committee may decide to require inclusion of this or other information explicitly as part of a written document provided to patients.

Children's Wisconsin SPECIFIC REQUIREMENTS

Physician Responsibilities when using a HUD at CW to treat a patient clinically:

- Obtain designated IRB (and CW HRPP approval - via local context review of the submission) and continuing approval at the frequency determined by the IRB of record.
    1. FDA regulations require a HUD to have IRB approval and oversight even if it's not research. It's different because safety and effectiveness is based on presumptions and not proven data. However, this is non-negotiable and is a violation of FDA regulations if you do not get prior IRB approval to use the HUD. The institution (CW) in which the HUD will be used must also agree to its use.
    2. When MCW pediatric IRB will be the reviewing IRB, the application is submitted via eBridge - selecting that this will be treatment use/HUD, and indicating it will be used at CW. If another IRB is being requested to serve as the IRB of record, a reliance request must be submitted in eBridge for CW HRPP consideration. The submission requirements of the reviewing IRB must be followed.

- Follow the requirements of the IRB of record as well as the CW HRPP
    - Refer to the CW HRPP manual for specifics regarding CW requirements for using a HUD in CW space

Parental Permission/Consent document - CW requirements

- Contact the CW HRPP office to request the HUD consent template.
- Because this is treatment use, assent of a minor patient is not required.
    - By policy, CW requires a consent form to be used, and this should be consistent with the HDE approved labeling and provide sufficient information in lay language for the patient/parent or legally authorized representative to make an informed decision regarding use.
    - It should be clear that effectiveness has not been demonstrated.
    - The consent does not need to contain all the elements of a research consent when the HUD is being used for treatment.
    - When a HUD is used for treatment, the consent/parental permission documents should NOT mention or imply a research activity
- Provide patients with information about the HUD (and obtain documented parental permission/consent if required by the CW HRPP and/or IRB of record)
- Report serious adverse events and deaths to the IRB of record **and** to the FDA using the Medical Device Reporting System at 21 CFR 803.

When does the use of a HUD become a clinical investigation?

- When data is being collected about the safety and effectiveness of the HUD and it is being used **outside of its approved indication**. It then becomes subject to 21 CFR

Part 56,21 CFR part 50, and the additional safeguards at 21 CFR 50, subpart D (additional protections for children).
    - In these cases, the HUD used is reviewed and approved by the IRB and the CW HRRP per the same review pathway and with the same requirements, as the review of any clinical investigation. This includes the need for assent/parental permission/consent documents that meet the same regulatory requirements and local requirements as for any research.
    - The IRB must apply the IDE rules at 21 CFR 812. Many times a HUD sponsor will have already obtained and FDA approved IDE before initiating the clinical investigation. However, if there is not IDE, then the IRB must make a SR or NSR device determination as per 21 CFR 812.66.
- When data is being collected about the safety and effectiveness of the HUD and it is being used **within its approved indication:**
    - The device is exempt from the FDA IDE Requirements under 21 CFR 812
    - The IRB is not required to make a SR or NSR determination.

Use of a HUD in an emergency situation

If a physician needs to treat a patient with a HUD in an emergency, the HUD may be used within its approved indications prior to IRB review only if approval cannot be obtained in time to prevent serious harm or death to the patient. If there is no alternative device for the patient's condition, in this situation the physician is obligated to

- Report the use to the IRB and the CW HRPP within five working days. This must be done in writing, submitted via the eBridge submission platform, and include:
    - patient information
    - reason for the use
    - date the HUD was used.
    - patient protection measures that were followed
- notify the HDE holder of its use and any adverse events that occur.
- report serious adverse events and deaths to the FDA and the IRB using the Medical Device Reporting System (MDR) at 21 CFR 803

Decision tree from the Mayo Foundation for Medical Education and Research, Humanitarian Use Devices for Clinical Treatment or Diagnosis.

Details regarding submitting a request to use a HUD at Children's Wisconsin - Diagnostic or Treatment Use

NOTE: When a HUD is being used as part of clinical investigation - requirements and submission process is the same as for any clinical investigation submitted for approval. This section applies to treatment use.

The health care provider seeking approval for diagnostic or treatment use of a HUD at CW facilities is responsible for obtaining IRB approval prior to use of the HUD at the facility and for complying with the applicable regulations, including those for medical device reporting, organizational policies, and the requirements of the IRB of record.

Health care providers seeking initial IRB approval for diagnostic or treatment use of a HUD for the indication(s) in the HUDs approved labeling should submit the following materials to the IRB via the eBridge electronic submission platform:

1. Application Form – Humanitarian Use Devices (non-research uses); **select treatment use/HUD in the smart form PRO in eBridge.**
2. A copy of the HDE approval letter from the FDA.
3. A description of the device, such as a device brochure.
4. The product labeling.
5. The patient information packet for the HUD.
6. The proposed clinical consent process (note: CW HRPP requires prospective written consent for HUDs when consent is possible; the HUD user can request an alteration with justification specific to the circumstances of device use); and
7. Other relevant materials (e.g., training certificates) as identified in the Application Form.

The IRB of record will review the proposal at a convened meeting, and will

- Ensure that appropriate expertise is available either within the membership in attendance or via the use of consultants.
- Review the risks to patients that are described in the product labeling and other materials.
- Review the proposed procedures to ensure that risks are minimized.
- Evaluate whether the risks are reasonable in relation to the potential benefits to patients at the facility; and
- Evaluate the patient information packet and proposed consent document and process and will determine if the materials are adequate and appropriate for the patient population and are consistent with CW's policy and expectation for informed consent.

NOTE: as with any submission for activities that will occur at CW, the CW HRPP will also review the requested use of the HUD for local context considerations. This will occur as an ancillary review prior to IRB committee review and must be approved for local context before it moves on to committee review.

The IRB (or the CW HRPP) may:

- specify limitations on the use of the device,
- require additional screening and follow up procedures,
- require interim reports.
- require continuing review more often than annually.
- set other conditions or requirements as appropriate to minimize risks to patients and ensure the safe use of the device in the facility.

Modifications to the treatment use of the HUD - submitted via eBridge electronic submission platform

Once use of the HUD is approved, the health care provider is responsible for submitting any proposed changes to the IRB-approved plan or patient materials and obtaining approval for those changes prior to implementation, unless the change is necessary to avoid or mediate an apparent immediate risk to a patient.

- Proposed changes may be submitted using the Amendment Form and should be accompanied by any revised materials or supporting documentation.
- The IRB may review these changes using expedited review procedures or refer the changes for review by the convened IRB.

Reporting Requirements for treatment use of the HUD

The health care provider is responsible for submitting reports to the FDA, the IRB of record and the manufacturer/HDE Holder whenever a HUD may have caused or contributed to a death, and must submit reports to the manufacturer (or to FDA and the IRB of record if the manufacturer is unknown) whenever a HUD may have caused or contributed to a serious injury (21 CFR 803.30 and 814.126(a)).

- Serious injury means an injury or illness that (1) is life-threatening, (2) results in permanent impairment of a bodily function or permanent damage to a body structure, or (3) necessitates medical or surgical intervention to preclude permanent impairment of a bodily function or permanent damage to a body structure (21 CFR 803.3).

- The specific requirements for this reporting are in the Medical Device Reporting (MDR) Regulation, at 21 CFR Part 803.
- The IRB of record will review these reports via either expedited or convened review, as appropriate, and will consider whether any changes are needed to the IRB-approved plan or patient materials.
- The CW HRPP will also review for any institutional concerns.

Continuing Review of treatment use of the HUD - submitted via eBridge electronic submission platform

The physician is responsible for submitting continuing review materials to the IRB sufficiently in advance of the expiration date, in accordance with CR submissions policy in the CHW HRPP SOP manual and per the policies of the IRB of record, to ensure IRB review and re-approval prior to expiration. Submission for continuing review MUST be submitted no later than 60 days before the date of expiration.

Materials to be submitted include:

1. The Continuing Review Report – Humanitarian Use Devices (non-research uses)
2. The most recent periodic report to the FDA by the HDE holder.
3. The current patient information packet, if applicable.
4. The current consent, if applicable.
5. Other materials as identified on the Continuing Review Report; and
6. Any other new relevant information or materials
7. The IRB may conduct continuing review using expedited review procedures or review by the convened IRB.

References:

- Institutional Review Board: Management and Function, 3rd ed. Editors Bankert, E; Gordon, B; Hurley, E; and Shriver, S
- US Code of Federal Regulations - 21 CFR 812, 21 CFR 50, 21 CFR 56
- CW HRRP SOP Manual