Humanitarian Use Device (HUD) FAQs: Considerations for Investigators and IRBs

1. **What is a Humanitarian Use Device (HUD)?**
    - A HUD is a legally marketed 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.
    - Requests for HUD designation are made to the FDA's Office of Orphan Products Development. Details of this process can be found at 21 CFR 814.102.
    - Use of the HUD under the *approved indication* does not constitute research (a clinical investigation) unless safety and efficacy data are being collected. (See question #8 below that addresses when use of a HUD is considered a clinical investigation.)
    - Within the NIH Intramural Research Program (IRP), approval by the convened IRB for use in the facility is required before a HUD can be used for clinical care (as part of medical practice), except for emergency situations. (See section below related to use of a HUD in emergency situations.)

2. **What is a Humanitarian Device Exemption (HDE)?**
    - An HDE is a marketing application for a HUD that provides a channel for manufacturers to develop devices to benefit small patient populations.
    - HDEs provide an exemption from the typical FDA requirements that are applied to most medical devices (for example those approved or cleared via the PMA or 510k path), when they are used in compliance with the FDA-approved indication(s).
    - To approve an HDE, the FDA must find that the device:
        - Will not expose patients to an unreasonable or significant risk of illness or injury and that the probable benefit outweighs the risk
        - Would not be available to a person without an HDE and no comparable device (other than another HDE or IDE) is available
        - The disease or condition affects not more than 8000 persons in the US annually.

3. **What are the responsibilities of the Humanitarian Device Exemption (HDE) Holder?**
    - Ensure that a HUD used under an HDE is administered only in institutions after an IRB has approved the use of the HUD for clinical care at that facility.
    - Notify the FDA of any withdrawal of approval for the use of a HUD by the Reviewing IRB within 5 working days after being notified of the withdrawal of approval.

4. **What should I know about use of HUDs for *clinical care (as part of medical practice)* at the NIH?**
    - NIH IRB approval of the use of the HUD in the facility (e.g., at the Clinical Center) must be obtained before it can be used at the NIH.
    - Once approved at the NIH, a HUD can be used according to its approved labeling and indication(s) to treat or diagnose patients. It can also be used "off label" as a part of medical practice. Note that if you are using it off label as part of medical practice, you **cannot** collect any research data about the safety or effectiveness of the device other than that data collected as part of the clinical care of that patient.
    - Following the approval of the use of the HUD at the NIH, the IRB does not need to review or be notified of each individual use of the HUD for clinical care.

- Once the HUD is approved for use at the NIH, it may be used *off-label* for clinical care (not research) without additional IRB notification or approval.
- For initial review of a HUD, the IRB must perform their review at a convened meeting, but subsequent reviews may be conducted by expedited procedures.
- The IRB will evaluate the risks to patients posed by the device, ensure that the risks are minimized and evaluate whether the risks are reasonable in relation to the proposed use of the device when it conducts initial review of a HUD. The IRB will also assess whether the proposed use of the device is consistent with the product labeling and HDE approval order as well as review any information that will be provided to the patient about the device (for example, the patient information sheet).

5. Is a consent form needed when a HUD will be used for *clinical care* and not for research purposes?

- The NIH IRB does not require that an informed consent document be submitted for approval and use.
- The NIH IRB does require that the treating physician provide the patient with an information sheet describing the HUD. This should be submitted to the IRB for review.
- The information sheet should be clear that effectiveness has not been demonstrated, it is a HUD, and it is approved by the FDA to either treat or diagnose the specific disease or condition.
- The information sheet should make no reference to research.

6. What information and/or documents will the convened NIH IRB review as part of a HUD submission when the intended use is for *clinical care*?

- Under FDA regulations (21 CFR 56.108), the convened IRB is required to initially review the HUD submission for use in a specific facility. The NIH IRB requires that the following information be submitted:
  - A copy of the FDA HDE approval
  - Device labeling
  - Any patient information sheet or brochure that may be available for the HUD or has been developed for use
  - A brief protocol that describes the device, the proposed use, patient population, screening procedures, and treatment plan as well as required unanticipated device reporting criteria

7. What additional considerations should the IRB be aware of when reviewing HUD submissions for *clinical care*?

When reviewing HUD submissions, IRB members should consider the following:

- Are risks minimized by using procedures that do not unnecessarily expose patients to risk, and are risks reasonable in relation to the device being used and its probable benefit?
- Are there adequate provisions to protect the privacy of the patients and the confidentiality of any data being collected?
- Is the device being used within the scope of the FDA HDE approval order?
- As no written consent is required at the NIH IRP, is the patient or LAR provided a patient information sheet or brochure for the device?

8. When would use of a HUD be considered a *clinical investigation*?

- The collection of safety and efficacy data about the HUD is considered a clinical investigation and is subject to FDA regulations relating to investigational devices (21 CFR 812), IRB review and informed consent (sections 21 CFR Part 56 and 21 CFR Part 50, respectively), as well as HHS regulations (45 CFR 46), as applicable.
- Clinical investigation of a HUD is research and must be reviewed and approved by an IRB.
    - If *safety and efficacy data* are collected about a HUD, and it is being ***used within its HDE-approved indication,*** no IDE is required (21 CFR Part 812). Therefore, no SR or NSR determination needs to be made by the IRB.
    - If the use of the HUD in the clinical investigation *is not within its HDE-approved indication*, the investigation is subject to the IDE rules at 21 CFR 812, and the IRB must make a determination as to whether the investigation is a non-significant risk (NSR) study requiring IRB submission only, or a significant risk (SR) study requiring submission to the FDA.
- When a HUD is used in a clinical investigation, investigators are required to report events to the study sponsor as described in the protocol and 21 CFR 812. In addition to other required reporting, investigators must report any unanticipated adverse device effect (UADE) to the sponsor as soon as possible but no later than 10 working days after the investigator first learns of the effect. If the UADE is also an actual or suspected unanticipated problem, it must be reported to the IRB within seven calendar days of an investigator becoming aware consistent with event reporting requirements in Policy 801, *Reporting Research Events*. A UADE is defined as "Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects."

9. When can a HUD qualify for *emergency use*?

- If a physician, in an emergency situation (i.e., patient has serious or immediately life-threatening condition necessitating use of the HUD), determines that IRB approval for the use of the HUD at the facility cannot be obtained in time to prevent serious harm or death to a patient, a HUD may be used without prior approval. In this situation:
    - The HDE holder may ship the HUD, based on the physician's certification of the emergent need.
    - FDA regulations require that physician provide such notification to the Chair of the IRB in writing within 5 days of the emergency use of the device. Such written notification must include the identification of the patient involved, the date on which the device was used, and the reason for the use.

10. Other than submitting my protocol to the IRB for continuing review, if applicable, are there other reporting requirements that I need to be aware of when using a HUD?

- If you are the HDE holder, you are subject to FDA's post approval reporting requirements which are described at 21 CFR 814.126.
- HDE holders and users must follow the FDA device reporting requirements as specified in 21 CFR 803.

11. Who do I contact for additional guidance about HUDs?

Contact the NIH Office of IRB Operations at irb@od.nih.gov or the Regulatory Support Section of the Clinical Center Office of Research and Compliance at REGSupportORSC@nih.gov for any questions or guidance you may require.

12. Where can I find additional information about HUDs?

FDA Resources

- 21 CFR 814 Subpart H-Humanitarian Use Devices
- Guidance Document- Humanitarian Use Device (HUD) Designations (2013)
- Guidance Document-Humanitarian Use Device Exemption Program (2019)
- Humanitarian Use Device (HUD) Designation Program
- Education and Media Resources for HUD Program
    - Chowdhury K. Humanitarian Use Device (HUD) Program Overview (slides)
    - Headlee D. Humanitarian Device Exemption (HDE): Overview and Pre-approval Activities (slides)
    - Headlee D. Humanitarian Device Exemption (HDE): Post-approval Activities (slides). Includes information about responsibilities of HDE holders and IRBs.

NIH Policy 501, Research Involving FDA Regulated Devices (Section E.5)

NIH Policy 801, Reporting Research Events

Craddock T. Humanitarian Use Devices. In *Institutional Review Board Management and Function*, EA Bankert, BG Gordon, EA Hurley, and SP Shriver (Eds), (2022), Jones and Bartlett Learning, Burlington, MA.