INSTITUTIONAL REVIEW BOARD (IRB) SUMMARY
MEDICAL DEVICES: HUMANITARIAN USE DEVICES (HUD)
(21 CFR PARTS 20 AND 814 SUBPART H 814.124, 2019 Draft HDE Guidance)

HUD CLINICAL USE QUICK POINTS

Clinical use of a Humanitarian Use Device (HUD) for treatment and diagnosis is not research.
Regulations require initial review by the convened IRB and continuing review (may be expedited) of clinical use of a HUD. **TIP:** If not provided, the HDE Approval Order is available online and it includes indications, summary of safety and probably benefit, labeling and consumer information for patients. http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2
The IRB device form may be used to describe the device and document the HDE number, plans to secure/label the device to ensure accountability, traceability and prevent unauthorized use, and describe any special qualifications and training specified in the HDE Approval Order to use or administer the HUD.
At its discretion, the IRB may require the clinician to complete the CITI HUD Training module to ensure he/she is aware of applicable regulatory responsibilities and IRB requirements. https://www.research.uky.edu/office-research-integrity/humanitarian-use-device-hud-training
The IRB may approve use of the device in general or apply any limitations to use (see below).
FDA does not require informed consent for clinical use of a HUD, however the IRB may choose to require informed consent or allow use of a modified clinical consent or operative permit. Information that may be included is detailed below but an important point is that, *FDA approves HUDs based on safety and probable benefit; therefore, effectiveness of the device for that use has not been demonstrated.*
If available, the healthcare provider should provide patients with the HDE holder's patient information packet found at https://www.fda.gov/medical-devices/hde-approvals/listing-cdrh-humanitarian-device-exemptions.
FDA's determination of safety and probably benefit is only within its approved indications. Use outside of the HUD approved indication (off-label clinical, emergency or compassionate use) or investigational use involves different requirements. (See description below or the IRB HUD SOP)

HUD SUMMARY

- A **humanitarian use device** (HUD) is a device that is intended to benefit patients by treating or diagnosing a disease or condition that affects or is manifested in fewer than 8,000 individuals in the United States per year.
- A HUD can be approved for marketing through a **humanitarian device exemption** (HDE). Unlike the premarket approval application (PMA), the HDE does not require clinical data demonstrating effectiveness. However, the HDE must contain sufficient information for the Food and Drug Administration (FDA) to determine that the probable benefit to health outweighs the risk of injury or illness.
- UK IRB requirements and procedures for use of a HUD are outlined in the IRB Humanitarian Use Device (HUD) Standard Operating Procedure (SOP)

HUD USE

General Requirements

- The term "**use**" refers to the use of a HUD for clinical care according to its approved labeling and indication. FDA has decided that a HUD which provides for marketing approval, does not constitute

"research" or an "investigation", however FDA has determined that clinical use of a HUD requires prospective IRB review and approval.

- Because a HUD is a legally marketed device, no systematic data is collected; however Medical Device Reporting (MDR) reports may provide risk and benefit information for continuing review.

- For many HDEs, the HDE holder is required to provide training on the use of the device prior to the health care provider using the device. Such requirements would be specified in the HDE approval order, available at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2.

- The healthcare provider responsible for the IRB approved HUD device should clearly label and store the device to ensure accountability and traceability and prevent use outside of designated sponsor or IRB restrictions/ limitations.

IRB Review

- As stated in 21 CFR 814.124(a), the humanitarian device exemption (HDE) holder must ensure that the HUD is administered only to patients at health care facilities having a duly constituted IRB as outlined in the FDA IRB regulations (21 CFR Part 56). The health care provider at such facilities is responsible for obtaining IRB approval before use of the HUD.

- Initial IRB approval should be performed at a convened IRB meeting and continuing review of the HUD is required in accord with IRB regulations 21 CFR Part 56. FDA allows continuing review to be conducted using the expedited review procedures (see 21 CFR 56.110) unless the IRB determines that convened board review should be performed.

- The IRB must have among its members (or consultants) the appropriate expertise to perform an adequate review of the use of a HUD at the institution. IRBs may defer in writing to another similarly constituted IRB that has agreed to assume responsibility for initial and continuing review of the use of the devices.

- 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 health care 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: (1) one or more measures of disease progression; (2) prior use of and failure of the alternative treatments; (3) reporting requirements to the IRB or IRB Chair; (4) appropriate follow-up precautions and evaluations, or; (5) any other criteria IRB determines to be appropriate.

The IRB may at its discretion choose to require new HUD users or HUD investigators to complete the CITI HUD Training Module. https://www.research.uky.edu/office-research-integrity/humanitarian-use-device-hud-training

Informed Consent

- Since use of a HUD according to its approved labeling is not research, FDA waives the requirements for informed consent. State law or local institutional policy may require informed consent. The IRB may choose to require informed consent when the IRB approves use of the HUD in a facility.

- If Informed consent is required, the form or process should include information from the HDE holder's patient information packet found at http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2. In addition, suggested content includes:
  - An explanation that the HUD FDA approves HUDs based on safety and probable benefit; therefore, effectiveness of the device for that use has not been demonstrated;
  - A description of any ancillary procedures associated with the use of the HUD;
  - A description of the use of the HUD;
  - Known risks or discomforts; an explanation of the postulated mechanism of action of the HUD in relation to the disease or condition; a statement indicating that the effectiveness of this device for this use has not been demonstrated; and a statement that the patients information may be shared with a sponsor or FDA. The IRB may decide to include other information.

- Even when the reviewing IRB does not require informed consent, the healthcare provider should provide patients receiving HUD with information from the HDE holder's patient information packet which may be obtained by selecting the HDE number on the FDA website (http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfHDE/HDEInformation.cfm#2).

EMERGENCY, OFF-LABEL CLINICAL USE, AND OFF-LABEL SINGLE-SUBJECT COMPASSIONATE USE OF A HUD OUTSIDE APPROVED INDICATIONS

- Physicians should be cognizant that FDA has made a determination of safety and probable benefit for use of the HUD only within its approved indication(s). If a HUD is used outside its approved indication(s) in an emergency or compassionate situation, the FDA recommends that the physician obtain informed consent from the patient and ensure that patient protection measures are followed.

- The UK IRB requires prospective IRB review and informed consent in a format appropriate for emergency, off-label or single-subject off-label compassionate use**.**

- For any off-label use, the healthcare provider includes the following with the IRB submission:
  - HDE holder documentation allowing off-label clinical use (if available) or attestation that use does not violate existing restrictions or limitations;
  - Justification for off-label clinical use;
  - Circumstances necessitating treatment with the HUD;
  - A discussion of why alternative treatments are unsatisfactory; and
  - Assurances and information about patient protection measures.

- Off-label emergency use, follows the same procedures that govern emergency use of an unapproved device and off-label single-subject compassionate use is requested via protocol exception (see HUD SOP).

- For emergency or compassionate use, the healthcare provider monitors the patient and submits a report of use to the HDE holder or FDA, including any safety related information.

HUD INVESTIGATIONS

- The term, "**investigational use**" is used when a HUD is being used in research to collect safety or effectiveness data.
- A HDE holder may collect safety and effectiveness data for the HDE-approved indications without an IDE. If the HUD is the subject of a clinical investigation (i.e. safety and effectiveness data will be collected), then IRB approval and informed consent is required because this is an FDA regulated

clinical investigation. If the HUD is studied in a clinical investigation, the elements included in the informed consent document must conform to the requirements found in 21 CFR 50.25.

- Clinical investigations of a HUD beyond its approved indication(s) (e.g. for a broader or off-label indication) must be conducted in compliance with 21CFR 812 requiring an IDE if significant risk(SR). IRB approval and research informed consent are required.

FDA GUIDANCE HUD

The above link provides guidance based solely on the FDA HUD regulations.

ADDITIONAL HDE REQUIREMENTS

- Holder of the humanitarian device exemption is required to notify FDA of the withdrawal of approval for a humanitarian use device by an IRB within five working days after being notified of the IRB action.

- HDE holders may charge for HUDs used clinically to treat or diagnose a patient. If specific eligibility criteria are met, the manufacturer may sell the device for profit within limits. If a HUD is studied in a clinical investigation of a new indication, the HDE holder may not charge subjects or investigators a price larger than necessary to recover the costs to manufacture, research, develop, and handle the HUD.

MEDICAL DEVICE REPORTING

All FDA-approved devices are subject to Medical Device Reporting (MDR) requirements as described in FDA regulations (21 CFR 803).

Clinicians and user facilities are required to submit medical device reports to the HDE holder, FDA, and IRB whenever a HUD may have caused or contributed to a death or serious injury, or has malfunctioned and would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

A *serious injury* means an injury or illness that:

1. Is life-threatening;
2. Results in permanent impairment of a body function or permanent damage to a body structure; or
3. Necessitates medical or surgical intervention to preclude permanent impairment of a body function or permanent damage to a body structure.

The HDE holder or manufacturer submits reports to the FDA and all reviewing IRB(s) within 10 working days based on the same criteria.

MDR provides a mechanism for the FDA and manufacturers to identify and monitor significant adverse events involving medical devices. The MAUDE database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers and device user facilities) and voluntary reporters such as health care professionals, patients and consumers.

- For investigational use of a HUD under an Investigational Device Exemption (IDE), reports of unanticipated adverse device effects (UADE) must be reported to the HDE holder, FDA, and IRB per the Unanticipated Problem and Safety Reporting Policy.

HIPAA

- The use of a HUD according to its approved labeling and indication is generally for treatment or diagnosis, even though such use requires IRB approval. If a HUD is being used according to its approved labeling and indication for treatment purposes, and not in a clinical investigation, then protected health information about a patient may be used or disclosed for treatment or diagnostic purposes without the patient's authorization under HIPAA.

- If a HUD is being used in a clinical investigation for research purposes, whether or not the use of the HUD is the subject of the investigation, then protected health information about a patient that is used or disclosed for purposes of the clinical investigation requires the patient's authorization under the HIPAA Privacy Rule. The IRB may waive this authorization if certain waiver criteria are met.

SUMMARY OF FEDERAL AND INSTITUTIONAL HUD REQIREMENTS

The table below summarizes requirements based on FDA guidance and UK Institutional Policy.
For details see the UK HUD SOP.

Condition	Regulatory Approval	IRB Approval Requirement(s)	Single case or Group Approval	Informed Consent Requirement
HUD *Use* (on label)	FDA approved for marketing under Humanitarian Device Exemption (HDE) based on safety and probable benefit.	FDA regulations require the healthcare provider to obtain approval from the convened IRB before use of a HUD.	IRB may approve the use of the device within the scope of the FDA-approved indications for groups of patients meeting clinical criteria.	FDA does not require informed consent for use of a HUD. The IRB may choose to require informed consent or allow use of a modified clinical consent or operative permit that is consistent with the approved labeling.
Emergency Use HUD	Healthcare provider assumes patient monitoring responsibilities of HDE holder, and reports the outcome of the emergency use including any safety related information to the HDE holder or the FDA.	The UK IRB requires prior review and confirmation that the case meets emergency use criteria by the IRB Chair or designee, unless immediate use is required and time is not sufficient. MD Submits a follow up report to the IRB within five working days of emergency use.	Single case	UK policy requires informed consent be obtained from patient or legally authorized representative (LAR) using IRB approved consent form or modified clinical consent or operative permit. Consistent with the UK Emergency Use SOP, if emergency situation requires use without informed consent, independent assessment from a qualified physician should be included in the five day report.
Off-Label Clinical or Single-Subject Compassionate Use HUD (outside approved indication)	Healthcare provider contacts the HDE holder to determine off-label use restrictions or limitations Healthcare provider reports any safety related information, to the HDE holder or FDA.	Off-label clinical use protocols are reviewed by the Convened IRB. Off-Label Single-Subject Compassionate Use is requested as a HUD protocol-exception	IRB may approve single-subject use or protocol where use is justified and not prohibited by HDE holder.	The UK IRB requires the healthcare provider to obtain informed consent from patient or LAR using an IRB approved consent form or modified clinical consent or operative permit.
***Investigational Use* of a HUD according to its approved labeling and indications**	A HDE holder may collect safety and effectiveness data **for the HDE-approved indications** without an IDE.	The investigator must obtain IRB approval for a HUD Investigation (21 CFR 56) and subpart D safeguards for children.	Either per protocol	Research informed consent is required as this is an FDA regulated investigation. (21 CFR 50)
***Investigational Use* of a HUD beyond its approved indication (new indication)**	An investigation of a HUD **for a different indication** must be conducted in compliance with the IDE regulations (21 CFR 812).	The investigator must obtain IRB approval for a HUD Investigation. The IRB will need to make a SR/NSR determination, unless already determined by	Either per protocol	Research informed consent is required as this is an FDA regulated investigation.

		FDA. (21 CFR 812)		

References:

Department of Health and Human Services, Food and Drug Administration, 21 CFR Parts 20 and 814
Department of Health and Human Services, Food and Drug Administration, SUBPART H – HUMANITARIAN USE DEVICES 814.100
FDA Final Guidance for HDE Holders, Institutional Review Boards (IRBs), Clinical Investigators, and FDA Staff
Humanitarian Device Exemption (HDE) Regulation: Questions and Answers, July 8, 2010
Humanitarian Device Exemption (HDE) Program Draft Guidance 2018

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