I. PURPOSE

The purpose of this SOP is to describe the submission requirements and process for IRB review of a Humanitarian Use Device (HUD), for clinical or investigational use.

II. POLICY STATEMENT

Clinical use of a HUD at CHOP requires approval prior to use by the CHOP IRB (or CHOP may rely on an outside IRB), with the exception of emergency use. Approval from the IRB is not required for each subsequent use, provided the use of the HUD is within the terms of the IRB approval. The IRB is also responsible for continuing review of the HUD.

Investigational use of a HUD (i.e. to establish safety and effectiveness of the HUD, regardless of whether it is being used in accordance with its HDE) needs to meet the requirements of all other relevant IRB SOPs governing human subjects research and must comply with 21 CFR 812.

III. SCOPE

This policy applies to the use of a HUD at CHOP.

IV. DEFINITIONS

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 not more than 8,000 individuals in the United States per year.
Devices that receive HUD designation may be eligible for marketing approval under an HDE application.

Humanitarian Device Exemption (HDE): A HUD under an HDE is exempt from the requirement of establishing a reasonable assurance of effectiveness that would otherwise be required under sections 514 and 515 of the FD&C Act. Approval of an HDE application under 21 CFR part 814, Subpart H, is considered "FDA approval" of the device based on, among other criteria, evidence that 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 account the probable risks and benefits of currently available devices or alternative forms of treatment.

HDE Holder: The HDE holder is responsible for ensuring that a HUD under an approved HDE is administered only in facilities having IRB oversight in accordance with the Agency's regulation governing IRBs (21 CFR 56).

Investigational Device Exemption (IDE): IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA, for significant risk devices) has

approved the sponsor's study application and all the requirements under 21 CFR 812 are met. An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution. An IDE is required for an investigational use of a HUD that is being used off label.

Medical Device Reports (MDRs): "MDR reportable events" are events that manufacturers become aware of that reasonably suggest that one of their marketed devices may have caused or contributed to a death or serious injury, or has malfunctioned and the malfunction of the device or a similar device that they market would be likely to cause or contribute to a death or serious injury if the malfunction were to recur.

Use: *Clinical Use* refers to use of the HUD, off label or in accordance with its label, for treatment or diagnosis as part of clinical care (not for research purposes). *Investigational use* refers to research/clinical investigation involving a HUD, off label or in accordance with its label.

V. PROCEDURES

A. Clinical use of a HUD for treatment or diagnosis in accordance with the approved label or off-label

A HUD marketed under an HDE is a legally marketed device, and its use in clinical care does not constitute "research."

1. Clinical use of a HUD for a single patient or a group of patients
   (a) Initial Review
      (1) The healthcare provider wishing to use the device will submit an application in eIRB. The documents required for initial IRB review include, but are not limited to, the following:
         i. A copy of the HDE approval order;
         ii. A description of the device;
         iii. The product labeling;
         iv. The patient information packet that may accompany the HUD;
         v. A sample consent form for the use of the HUD (a clinical consent suffices); and
         vi. A summary of how the healthcare provider proposes to use the device, including a description of any screening procedures, the

HUD procedure, and any patient follow-up visits, tests or procedures. The IRB does not require submission of a protocol.

vii. For off-label uses, the submission must also include:

a. Documentation from the HDE holder allowing off-label clinical use (if available), or an attestation that the use does not violate existing restrictions or limitations;

b. A justification for the off-label use (including why treatment using the HUD is necessary and why alternative treatments are unsatisfactory);

c. Schedules to monitor the patient(s) (taking into consideration the patient(s)'s specific needs); and

d. Information about the risks and probable benefits of the device for the proposed subject population.

(2) Initial review and approval need to be conducted by the convened board. The IRB will review the study at the convened board in accordance with the 'Categories of Action' SOP (IRB SOP 406).

(3) In its review, the IRB will consider the healthcare provider's qualifications through training and expertise to use the device (the IRB may rely on the Department/Division approver's assessment of the qualifications and credentials). The IRB may specify limitations on the use of the device based upon one or more measures of disease progression, prior use and failure of any alternative treatment modalities, reporting requirements to the IRB, and appropriate follow-up precautions and evaluations.

(b) Continuing Review

(1) The Continuing Review submission must be reviewed and approved by the IRB prior to the expiration date in order for activities to continue.

(2) Continuing review may be conducted using expedited procedures in accordance with the 'Continuing Review of Approved Research' SOP (IRB SOP 404). The reviewer(s) will consider the risk and benefit information available and any MDRs.

(c) Amendments

(1) A healthcare provider IRB-approved to use a HUD may submit a single subject amendment for compassionate use in a single subject (if not in accordance with the approved clinical use), in accordance with the

Amendments and Reports of New Findings to Approved Research SOP (IRB SOP 403).

(d) Adverse Event Reporting

(1) For a device approved under an HDE application, medical device reports (MDRs) submitted to FDA in compliance with the requirements of 21 CFR part 803 shall also be submitted to the Reviewing IRB.

i. MDRs must be submitted to the IRB when information reasonably suggests that a HUD may have caused or contributed to the death of a patient at CHOP.

ii. MDRs must also be submitted to the IRB if the manufacturer is unknown, and information reasonably suggests that a HUD may have caused or contributed to a serious injury (as defined by 21 CFR 803.3(w)) to a patient at CHOP.

2. Emergency use of a HUD for clinical care in a single patient

- The subject is confronted by a serious or immediately life-threatening disease or condition necessitating the use.
- No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
- There is either insufficient time to contact the Chair or Vice-Chair CPHS, or the Chair or Vice-Chair CPHS has confirmed that there is insufficient time for the IRB to meet and approve the use.

(a) The healthcare provider is required to comply with the requirements of the 'Exemption to the Requirement for Prior IRB Approval for Emergency Use of Investigational Drugs, Biologics, or Devices' SOP (IRB SOP 802, V.C.1-3, and 5)).

(b) The IRB will review the 5-day report in accordance with IRB SOP 802.

Note: The IRB's approval for the "use" of a HUD at CHOP to treat or diagnose patients in the course of providing clinical care does not mean that there has been IRB approval of a clinical investigation involving the HUD.

B. Investigational use of a HUD in accordance with the approved label or off-label

A clinical investigation of a HUD (i.e. to establish safety and effectiveness of the HUD) needs to meet the requirements of all other relevant IRB SOPs governing human subjects research, regardless of whether it is used in accordance with the approved label or used off-label. A clinical (hospital) consent is not sufficient for investigational use.

1. Investigational use in accordance with the approved label to collect safety and effectiveness data
   (a) The investigator will submit an application in eIRB in accordance with the Research Submission Requirements SOP (IRB SOP 301).
   (b) The IRB will review the study at the convened board in accordance with the 'Categories of Action' SOP (IRB SOP 406).
2. Investigational use off label
   (a) The investigator will submit an application in eIRB in accordance with the 'Research Submission Requirements' SOP (IRB SOP 301).
   (b) The IRB will review the study at the convened board in accordance with the Categories of Action SOP (IRB SOP 406) and the 'Determination of IND/IDE Requirement' SOP (IRB SOP 409). The proposed use will need to be in compliance with FDA regulations under 21 CFR 50, 56, and 812 (e.g., may require submission of an IDE application to FDA or be conducted under the abbreviated requirements for NSR devices at 21 CFR 812.2(b)).
3. Continuing Reviews, Amendments and Adverse Event Reporting will need to be submitted and reviewed in accordance with IRB SOPs 403, 404, and 408.

VI. APPLICABLE REGULATIONS AND GUIDELINES

21 CFR 50	21 CFR 56
21 CFR 803	21 CFR 812
21 CFR 814	
Guidance for Industry and Food and Drug Administration Staff; Humanitarian Device Exemption (HDE) Program (CDRH, September 2019)	Guidance for Industry and Food and Drug Administration Staff; Humanitarian Use Device (HUD) Designations (CDRH, September 2019)

VII. REFERENCES TO OTHER APPLICABLE SOPS

SOP 301: Research Submission Requirements	SOP 403: Amendments and Reports of New Findings
SOP 404: Continuing Review of Approved Research	SOP 406: Categories of Action
SOP 408: Unanticipated Problems Involving Risks to Subjects	SOP 409: Determination of IND/IDE Requirement
SOP 802: Exemption to the Requirement for Prior IRB Approval for Emergency Use of Investigational Drugs, Biologics, or Devices	

VIII. RESPONSIBILITIES

Title	**Responsibility**
Director, HSR	The Director, HSR (or designee) is responsible for reviewing incoming submissions and conducting preliminary review for either clinical or investigational use of a HUD.
Chair, CPHS	The Chair (or designee) is responsible for ensuring the appropriateness of all IRB decisions and actions regarding the clinical or investigational use of a HUD.

IX. ATTACHMENTS

The eIRB system contains all forms required to submit proposed uses of a HUD, continuing reviews, amendments and reportable events.

X. REVISIONS:

02-08-2021: Initial Approval Date:

06-09-2022: Revised to make minor administrative edits

XI. APPROVAL

Approval Indicator: Approved by Amy Schwarzhoff and Barbara Engel on 06/09/22

Amy Schwarzhoff, Director, Human Subjects Research and Barbara Engel, Chair, CPHS