Signatures and Dates:

Signature on file

Author:	Human Subjects Protection Branch	Date
QA Review	Human Subjects Protection Branch	Date
Approving Authority:	Human Subjects Protection Branch	Date

Review/Approval for unchanged documents

	Author/Date	QA Review/Date	Approving Authority/Date
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1. **Purpose and Applicability**

   This Standard Operating Procedure (SOP) documents the process used by the Walter Reed Army Institute of Research (WRAIR) Institutional Review Board (IRB) to review submissions regarding a Humanitarian Use Device (HUD). IRB review and approval is required for this use. As the WRAIR is not a military treatment facility (MTF), WRAIR will rely upon the IRB that has jurisdiction where the device will be used (e.g. DOD medical centers) for IRB review.

2. **Responsibilities**

   a. The WRAIR IRB members/WRAIR IRB Chair (or Designee) are responsible for:

      1) Reviewing the HUD request according to the procedures outlined in this SOP and Food and Drug Administration (FDA) guidance.

      2) Reviewing the appropriate pediatric information submitted by investigators and sponsors as part of the submission of a HUD, if applicable.

      3) Issuing approval or disapproval decisions to the investigator(s).

   b. The WRAIR Human Subjects Protection Branch (HSPB) Director and HSPB staff are responsible for:

      1) Verifying the HUD request is complete.

      2) Reviewing the appropriate pediatric information submitted by investigators and Sponsor(s) as part of the submission of a HUD, if applicable.

      3) Ensuring that the protocol materials are complete for submission to the WRAIR IRB for review.

   c. The Institutional Official (IO) or Designee is responsible for reviewing the HUD request and issuing final authority to execute it, if appropriate.

3. **Investigator Guidance**

   The Principal Investigator (PI) is expected to:

   1) Submit a protocol submission packet to the WRAIR IRB via the WRAIR HSPB (Refer to WRAIR SOP UWS-HP-623, Submission Requirements).

   2) Respond to requests for documentation and information from the WRAIR IRB and WRAIR HSPB.

3) Comply with the terms of approval from the IRB and IO.

4) Consult with the US Army Medical Research and Development Command (USAMRDC) Office of Regulated Activities (ORA) when the Humanitarian Device Exemption (HDE) holder is the Office of The Surgeon General (OTSG) or when the HDE applicant is Army personnel.

5) Maintain correspondence with the FDA and reviewing IRBs.

4. Materials and Equipment

Not Applicable

5. Procedures

a. Review and approval by a fully convened IRB is required before use of a HUD, as is WRAIR IO approval authorization prior to implementation. US Army Medical Research and Development Command (USAMRDC) component-level administrative review may also be required for use of HUD in certain populations, per USAMRDC Policy Memorandum 2018-75.

b. Investigators and Sponsors must provide the following documents to the IRB for review when submitting a HUD request:

1) Protocol submission packet (Refer to WRAIR SOP UWS-HP-623, Submission Requirements).

2) US Food and Drug Administration (FDA) HDE Letter allowing use of the HUD.

3) Summary of Safety and Probable Benefits (from Sponsor).

4) Labeling for the device.

5) Adverse event reporting requirements and device defect reporting requirements, to include providing updated information on a periodic basis demonstrating that the HUD designation is still valid, based on the most current and authoritative information available [21 Code of Federal Regulations (CFR) 814.126(b)]. As part of these reporting requirements, the number of devices shipped or sold since initial HDE marketing approval must also be reported [21 CFR 814.126(b)(1)(iii)].

6) To help FDA track information required for annual reporting to Congress, premarket approval of medical devices should include requirements relating to the submission of information on pediatric subpopulations that suffer from

the disease or condition that a device is intended to treat, diagnose, or cure, as required by the act, section 515A(a), Premarket Approval; General Requirements. FDA has concluded that the term 'pediatric patient' refers to patients who are 21 years of age or younger at the time of the diagnosis or treatment. Any request to the FDA for a humanitarian device exemption (HDE) should include information on the pediatric subpopulation. For a list of the specific information required, see the related sections in 21 CFR 814. Failure to submit the appropriate pediatric information can slow, or even stop, an FDA review.

7) FDA Annual Reports of HUD and continuing review reports.

8) Number of devices shipped or sold. If the number exceeds 8,000, an explanation and estimate of the number of devices used on multiple patients with a basis for the estimate.

9) Information describing the applicant's clinical experience with the device, any training completed or required, and a list of physicians who will be using the device.

10) A statement from the investigator concerning whether or not state law and / or institutional policy requires informed consent.

11) Any agreements [Memorandum of Agreement (MOA), Memorandum of Understanding (MOU), Cooperative Research and Development Agreements (CRADA), IRB Authorization Agreements (IAA), Funding specifications, etc.].

12) Additional IRB approvals from collaborating sites.

13) Patient Information Sheet (prepared by the Investigator or Sponsor), which is also referred to as "patient labeling," that meets the following requirements:

    a) Lay language (8th grade readability scale) used to inform the patient about the intended uses of the device (including that it is a HUD 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, relevant warnings, precautions, side effects and contraindications, and a statement that the effectiveness of the device has not been demonstrated.

    b) Who to contact for questions about the device (investigator's contact information).

14) Any advertisements or other descriptive materials used by the HDE holder or private label distributor.

Note: The Sponsor is responsible for post approval reporting requirements under 21 CFR 814.84 and 814.126.

c. The WRAIR IRB will review the submission following the review criteria in 21 CFR 56.111 and elsewhere in part 56, where applicable, and determine if informed consent is required. The WRAIR IRB may also require that the subject sign and date the Patient Information Sheet prior to the HUD use.

d. At the time of initial review, the WRAIR IRB will determine if approval of the use has any further restrictions on a case-by-case basis (such as: use of the device will be under a protocol). IRB approval may not exceed the scope of the FDA approved indication.

e. At the time of initial review, the IRB will determine if continuing review may be expedited (per 21 CFR 56.110) for an approved device or if full board review is required.

f. Investigators submit a continuing review report to the WRAIR IRB at a time frame determined by the IRB, but at least annually. This report will include information describing the applicant's clinical experience(s) with the device.

g. Investigators must submit the following to the WRAIR IRB:

1) Any amendments or supplements to the HDE.

2) FDA Annual Reports from the Sponsor.

3) Medical device reports (MDRs), safety reports and unexpected/unanticipated adverse events or unanticipated problems.

4) Increases in the incidence of anticipated adverse events.

5) Information reasonably suggesting that 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.

6) Reports of device failures necessitating a labeling, manufacturing or device modification.

7) Any further results of animal / laboratory or clinical testing, when appropriate.

8) Notification from the FDA regarding the suspension or withdrawal of the HDE.

9) Any withdrawal of approval by a reviewing IRB.

10) Final report from Sponsor.

11) Final report from investigator.

h. If the HUD is used in an emergency situation ("off label") to save the life or protect the physical well-being of a patient, conditions defined in the CFR must be met for emergency use. (Refer to WRAIR SOP UWS-HP-607, Emergency Use Notification and Reporting Procedures).

i. If the HUD is used for compassionate use, refer to WRAIR SOP UWS-HPO-604, Compassionate Use.

6. **Explanation of Abbreviations, Acronyms, and Definition of Terms**

Note: Abbreviations and acronyms have been defined in the text at the time of first use.

Institutional Review Board: A committee that has been formally designated to review, approve, and monitor biomedical and behavioral research involving humans with the aim to protect the rights and welfare of the research subjects (see Army Regulation 70-25, Appendix C-1). Selection for the board is in accordance with Federal guidelines outlined in 21 CFR 56.107, 32 CFR 219, and 45 CFR 46.

Research: A systematic investigation, including research development, and testing and evaluation, designed to develop or contribute to generalizable knowledge (32 CFR 219.102d).

Research Involving Human Subjects: Activities that include both a systematic investigation designed to develop or contribute to generalizable knowledge AND involve a living individual about whom an investigator conducting research obtains data through intervention or interaction with the individual, identifiable private information, or identifiable biospecimens.

Risk: The probability of harm or injury (physical, psychological, social or economic) occurring as a result of participation in a research study.

Serious Injury: 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 (21 CFR 803.3).

Sponsor: An individual, company, institution or organization that takes responsibility for the initiation, management, and/or financing of clinical research (ICH E6). The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. The USAMRDC Principal Assistant for Acquisition (PAA) serves as the Sponsor's Representative when programs within USAMRDC initiate the development of a new experimental product and conduct clinical investigations with the new experimental product. There are no sponsor-investigators in the USAMRDC.

7. References

Reference Number or Authors	Document Title
AR-40-68	Clinical Quality Management
AR-40-7	Use of Food and Drug Administration- Regulated Investigational Products in Humans Including Schedule I Controlled Substances
WRAIR IRB Charter	Walter Reed Army Institute of Research (WRAIR) Institutional Review Board (IRB) Charter
WRAIR HRPP	WRAIR Human Research Protection Program (HRPP)
ICH E6(R2)	Guideline for Good Clinical Practice
USAMRDC Policy	Command Policy Memorandum 2018-75
Titles 21, 32 and 45	Code of Federal Regulations

U.S. FDA	Humanitarian Device Exemption (HDE) Program, Guidance for Industry and FDA Staff, 06 September 2019
U.S. FDA	Guidance for Industry and FDA Staff, Humanitarian Use Device (HUD) Designations, 24 January 2013
SOP UWS-HP-623	Submission of Protocol Documents and Consent Forms for Review
SOP UWS-HP-607	Emergency Use Notification and Reporting Procedures
SOP UWS-HP-604	Compassionate Use

7. **Appendices and Attachments**

Appendix or Attachment Number	Title
None	

8. **Document Revision History**

Version Number	Brief Description of Changes	Effective Date
.00	New	18 Dec 2006
.01	Biennial review, including organization name updates, updates to procedures and references, and minor editorial clarifications.	08 April 2011
.02	Review and revisions to incorporate updated guidance, policies, regulations, and minor editorial clarifications	30 Jan 2020