Section 6: FDA Regulated Research/Drugs & Devices

6.1 Research Involving Investigational and Marketed Drugs

1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for research involving investigational and marketed drugs.

2.0 Policy

- 2.1. It is the policy of the Organization that the IRB will review all research involving the use of investigational drugs, biologics, and marketed drugs (test articles) in full accordance 21 CFR 50, 56; 21 CFR 312, 314; and 45 CFR 46, and with HRPP policies.
- 2.2. It is the policy of the Organization that investigators will conduct such research in full accordance with 21 CFR 50, 56; 21 CFR 312, 314; and 45 CFR 46, and with HRPP policies.
- 2.3. It is the policy of the Organization that sponsors and any CRO acting on behalf of the sponsor will fully comply with FDA regulations at 21 CFR 312.50-59

3.0 Definitions

- 3.1. Investigational Drug means: a) a drug or a biologic that is used in a clinical investigation under an Investigational New Drug (IND) Application, or b) a marketed drug that is being studied for an unapproved or approved use in a clinical trial.
- 3.2. Clinical Investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under Section 505(i) or 520(g) of the Food, Drug and Cosmetics Act or need not meet the requirements for prior submission to the FDA under these sections of the Act but the results of which are intended to be later submitted as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, and clinical investigation are deemed to be synonymous.
- 3.3. Investigator means the individual under which immediate direction the test article is administered or dispersed to a subject (21 CFR 56.102(h)). Under HRPP policy 1.26 (PI Qualifications and Responsibilities), this individual is referred to as the Principal Investigator (PI).
- 3.4. Human Subject means an individual who is or becomes a participant in a clinical investigation either as a recipient of the test article or as a control. A subject may be either a patient or a healthy individual.
- 3.5. Investigational New Drug (IND) Application is an application submitted to FDA to conduct a clinical investigation with an investigational drug that is subject to 21 CFR 312.2(a). The IND is

submitted by the sponsor of the research.

- 3.6. Marketed Drug is a drug or biologic approved by FDA for marketing and is generally in use for treatment purposes.
- 3.7. Sponsor is a person or organization who takes responsibility for and initiates a clinical investigation. The sponsor may be a pharmaceutical company, governmental agency, academic institution, private organization or an individual investigator.
- 3.8. Sponsor-Investigator is an individual that both initiates and conducts an investigation. Additionally the sponsor-investigator directs the administration or dispensing of the investigational drug. An investigator who also serves as a sponsor must comply with all FDA requirements applicable to both an investigator as well as a sponsor.
- 3.9. Emergency Use is the use of a test article on a human patient in a life-threatening or severely debilitating circumstance where no standard medically acceptable treatment is available and there is not sufficient time to obtain full IRB approval for use of the test article to treat the patient.
- 3.10. Expanded Access is the use of an investigational agent outside of a clinical trial. The terms expanded access and treatment use are used interchangeably to refer to use of an investigational drug when the primary purpose is to diagnose, monitor, or treat a patient's disease or condition. The term compassionate use is also occasionally used in the context of the use of an investigational drug to treat a patient. Although these terms have been used informally they are not defined or described in FDA regulations.

4.0 Procedures

- 4.1. All contracts between sponsors and UNMC, Nebraska Medicine, and BMC for Administration (SPA) or by UNeHealth, in compliance with HRPP policy 1.12 (Sponsored Research).
- 4.2. All contracts between sponsors and CHMC for investigational drug studies must be reviewed and approved by UNMC Sponsored Programs Administration (SPA) or by UNeHealth, or by CHMC Administration, in compliance with HRPP policy 1.12 (Sponsored Research). If the contract is reviewed and approved by CHMC Administration it will also be reviewed by UNMC SPA to assure the requirements of HRPP policy 1.12, section 4.3 are met.
- 4.3. The Organization has determined clinical investigations involving drugs should be reviewed by the full IRB in accordance with HRPP policy 2.2 (Full IRB Review). However, the IRB may determine select clinical investigations involving no more than minimal risk may be eligible for expedited review in accordance with HRPP policy 2.3 (Expedited Review).
- 4.4. If the contract agreement requires compliance with ICH GCP, the IRB will review the submission in accordance with HRPP policy 1.13 (Compliance with ICH-GCP). The investigator will designate the need for ICH GCP compliance in the IRB application.
- 4.5. The IRB will review the information in the application to ensure that investigational drugs are securely stored and dispensed in accordance with FDA regulations at 21 CFR 312.60-62.
  - 4.5.1. For research conducted at UNMC and Nebraska Medicine investigational drugs must be stored and dispensed in accordance with Investigational Drug Policies (I380 and MS05) which describe in-patient and out-patient requirements.
  - 4.5.2. For research conducted at CH&MC investigational drugs must be stored and dispensed in accordance with CH&MC Policy 204.00.
  - 4.5.3. For research conducted at an external site, a copy of the policy of the external site(s) which satisfies the requirements of FDA regulations at 21 CFR 312.60-62 must be submitted to the ORA.
- 4.6. Any PI who has a study that will be audited by the sponsor, a CRO or FDA must immediately notify the designated IRB Administrator and the UNMC Chief Compliance Officer. The IRB must be provided with a copy of the report following the audit.
- 4.7. When a study is audited by the Fred & Pamela Buffett Cancer Center Protocol Review Monitoring System (PRMS) Audit Committee, a copy of the report must be provided to the IRB.
- 4.8. The PI must promptly inform the IRB and Investigational Drug Pharmacist when a study

involving investigational drugs has been terminated.

5.0 Studies Requiring an IND

- 5.1. Prior to IRB approval of the study, the IRB will ensure that a valid IND is in effect for any drug study subject to 21 CFR 312.2(a). Documentation of the IND could be the industry sponsored protocol with the IND number, written determination from the FDA, or other documentation or communication verifying the IND number.
  - 5.1.1. The IND goes into effect 30 days after the FDA receives the IND unless the sponsor receives earlier notice from the FDA. If the FDA has not issued correspondence indicating the IND is in effect, the IRB will obtain the FDA communication from the Investigator regarding the IND submission. The IRB will not issue approval until either an FDA letter indicating the IND is in effect or until 30 days have passed since submission to the FDA.
- 5.2. If a study involves an investigator-initiated IND, it is the expectation of the Organization that the PI will also comply with the FDA-mandated sponsor requirements (21 CFR 312.50) and certify compliance by submitting Addendum O (Principal Investigator Responsibilities: Investigator-Initiated Drug Trials) which specifies all of the responsibilities of the Sponsor-Investigator.
- 5.3. For studies involving marketed drugs for potential new indications or changes in dose, an IND is required in accordance with 21 CFR 312.2(b)(1).
- 5.4. All protocol-related documents, including FDA notification, must contain matching IND numbers.
- 5.5. A clinical investigation involving an exception to the informed consent requirement under 21 CFR 50.24 must be performed under a separate IND (even if an IND for the same drug product already exists (21 CFR 50.24(d)).
- 5.6. If the IRB has any question or concern about whether an IND is required, the PI will be instructed to contact the Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER) or the Center for Biologics Evaluation and Research (CBER) to obtain a written determination.
  Note: If FDA regulated research involving an investigational drug is conducted outside of the US an IND is not required provided the study is conducted in accordance with GCP guidelines and FDA is able to validate the data from the study through an on-site inspection if FDA deems it necessary.

6.0 Exemptions from IND Requirements

- 6.1. A clinical investigation of a drug product that is lawfully marketed is exempt from the requirements of an IND if:
  - 6.1.1. The investigation is not intended to be reported to FDA in support of a new indication for use or any other significant change in the labeling for the drug; AND
  - 6.1.2. The investigation is not intended to support a significant change in the advertising for the product; AND
  - 6.1.3. The investigation does not involve a route of administration or dosage level or use in a patient population or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug; AND
  - 6.1.4. The investigation is conducted in compliance with 21 CFR 50, 56, and 21 CFR 312.7 (Promotion of investigational drugs)
- 6.2. A clinical investigation involving blood grouping serum, reagent red blood cell and anti-human globulin is exempt from the requirements of an IND if the conditions of (a) it is intended to

be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure, and (b) it is shipped in compliance with 312.160 (per 21 CFR 312.2(b)(2)).

- 6.3. A drug intended solely for tests in vitro or in laboratory research animals is exempt from the requirements of an IND if it is shipped in accordance with 21 CFR 312.160 (per 21 CFR 312.2(b)(3))
- 6.4. A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND (21 CFR 312.2(b)(5)).

7.0 Expanded Access to Investigational Drugs

- 7.1. FDA regulations at 21 CFR 312.300 (subpart I) allow certain individuals not enrolled in clinical trials to obtain expanded access to investigational drugs through various expanded access programs (EAPs).
  - 7.1.1. All expanded access programs must meet the basic criteria in 21 CFR 312.305(a). Specifically the FDA must determine:
    - 7.1.1.1. The patient or patients to be treated have a serious or immediately life-threatening disease or condition, and there is no comparable or satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition;
    - 7.1.1.2. The potential patient benefit justifies the potential risks of the treatment use and those potential risks are not unreasonable in the context of the disease or condition to be treated; and (3) Providing the investigational drug for the requested use will not interfere with the initiation, conduct, or completion of clinical investigations that could support marketing approval of the expanded access use or otherwise compromise the potential development of the expanded access use.
  - 7.1.2. All expanded access programs described below require prior IRB approval and informed consent of the subject.
  - 7.1.3. Specific EAPs:
    - 7.1.3.1. Single (Individual) Patients
      - 7.1.3.1.1. Treatment is generally limited to a single course of therapy for a specified duration, though FDA may authorize multiple courses or chronic therapy. Use of this EAP requires an individual patient IND for treatment use.
      - 7.1.3.1.2. The following determinations must be made (21 CFR 312.310):
        - 7.1.3.1.2.1. The requesting physician determine the probable risk to the person from the investigational drug is not greater than the probable risk from the disease or condition
        - 7.1.3.1.2.2. FDA must determine that the patient cannot obtain the drug under another IND or protocol
    - 7.1.3.2. Intermediate-Size Patient Populations
      - 7.1.3.2.1. Investigational drug may be used for the treatment of a patient population smaller than that typical of a treatment IND or treatment protocol, as per 21 CFR 312.315.
      - 7.1.3.2.2. The FDA must determine:
        - 7.1.3.2.2.1. There is enough evidence that the drug is safe at the dose and duration proposed for expanded access use
        - 7.1.3.2.2.2. There is at least preliminary clinical evidence of effectiveness of the drug, or of a plausible pharmacologic effect of the drug to make expanded access use a reasonable therapeutic option in the anticipated patient population.
    - 7.1.3.3. Treatment IND or Treatment Protocol (widespread treatment use)
      - 7.1.3.3.1. FDA may permit widespread use of an investigational drug under 21 CFR 312.320
      - 7.1.3.3.2. FDA must determine:
        - 7.1.3.3.2.1. The drug is being investigated in a controlled clinical trial

under an IND designed to support a marketing application for the expanded access use, or all clinical trials of the drug have been completed;
        - 7.1.3.3.2.2. The sponsor is actively pursuing marketing approval of the drug for the expanded access use with due diligence
        - 7.1.3.3.2.3. When the expanded access use is for a serious disease or condition, there is sufficient clinical evidence of safety and effectiveness to support the expanded access use; or when the expanded access use is for an immediately life-threatening disease or condition, the available scientific evidence, taken as a whole, provides a reasonable basis to conclude that the investigational drug may be effective for the expanded access use and would not expose patients to an unreasonable and significant risk of illness or injury.
    - 7.1.3.4. Group C Treatment IND
        - 7.1.3.4.1. “Group C” is a special class of Treatment IND that has been established by the FDA and the National Cancer Institute (NCI) for the distribution of certain investigational agents (generally Phase 3 study drugs) to oncologists for the treatment of cancer under protocols outside the controlled clinical trial. Group C drugs are distributed only by the National Institutes of Health (NIH) under NCI protocols.
        - 7.1.3.4.2. Though the FDA has generally granted a waiver from the IRB review requirements (21 CFR 56.105) the Organization has decided to require review and approval by the convened IRB in accordance with HRPP policy 5.2 (Waiver or Alteration of Informed Consent and HIPAA Authorization).
    - 7.1.3.5. Parallel Track Policy
        - 7.1.3.5.1. The FDA’s “Parallel Track” policy facilitates early access to promising new drugs for AIDS/HIV related diseases under a separate expanded access protocol that “parallels” the controlled clinical trials that are essential to establish the safety and effectiveness of new drugs.
- 7.2. Although an investigational article used under the FDA expanded access mechanism is intended for the purpose of clinical treatment, the FDA may consider the treatment to constitute a “clinical investigation” (i.e., research), and require that data from the treatment be reportable in a marketing application. Conversely, under the U.S. Department of Health and Human Services (HHS) human research protection rules, patients who receive investigational articles through the expanded access mechanism are not considered research subjects, and outcomes of expanded access treatments may not be included in reports of research funded by federal agencies that follow HHS rules.

8.0 Emergency Waiver of IND

- 8.1. FDA regulations at 21 CFR 312.310(d) address the need for an investigational drug to be used in an emergency situation that does not allow time for submission of an IND. The FDA may authorize shipment of the drug for a specific use in such a circumstance in advance of submission of an IND.
- 8.2. Prospective IRB review is required unless the conditions for exemption are met (21 CFR 56.104(c) and 56.102(d)). Informed consent is required unless the conditions for exemption are met (21 CFR 50.23).

9.0 Emergency Use of Investigational Drugs

Emergency use of an investigational drug will be administered to subjects in accordance with HRPP policy 6.4 (Emergency Use of a Test Article).

10.0 Waiver of Informed Consent for Planned Emergency Research

Waiver of informed consent for planned emergency research will be reviewed and approved by the full IRB in accordance with HRPP policy 5.6 (Exception from Informed Consent Requirements for Emergency Research).

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6.2 Research Involving Investigational and Marketed Devices

1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for research involving investigational and marketed devices.

2.0 Policy

- 2.1. It is the policy of the Organization that the IRB will review all research involving investigational devices and FDA-approved devices (test articles) in full accordance with the following: 21 CFR 50, 56; 21 CFR 812, 814; 45 CFR 46.
- 2.2. It is the policy of the Organization that investigators will conduct such research in full accordance with the above cited regulations and applicable HRPP policies.
- 2.3. It is the policy of the Organization that sponsors and any CRO acting on behalf of the sponsor will fully comply with FDA regulations at 21 CFR 812.

3.0 Definitions

- 3.1. Investigational Device means a device, including a transitional device, which is the object of a clinical investigation. As further defined, a device is any healthcare product that does not achieve its primary intended purpose by chemical action or by being metabolized.
- 3.2. Clinical Investigation means any experiment that involves a test article and one or more human subjects, and that either must meet the requirements for prior submission to the FDA under Section 505(i) or 520(g) of the Act or need not meet the requirements for prior submission to the FDA under these sections of the Act but the results of which are intended to be later submitted as part of an application for a research or marketing permit. The terms research, clinical research, clinical study, and clinical investigation are deemed to be synonymous.
- 3.3. Investigator means the individual under which immediate direction the test article is administered or dispersed to a subject. Under HRPP policy 1.26 (PI Qualifications and Responsibilities), this individual is referred to as the PI.
- 3.4. Human Subject means an individual who is or becomes a participant in a clinical investigation either as a recipient of the test article or as a control. A subject may be either a patient or a healthy individual.
- 3.5. Significant risk device (SRD) is a device that
  - 3.5.1. Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; or
  - 3.5.2. Is purported or represented to be for a use in supporting or sustaining human life and

presents a potential for serious risk to the health, safety, or welfare of a subject; or
    - 3.5.3. Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety or welfare of a subject; or
    - 3.5.4. Otherwise presents a potential to the health, safety or welfare of a subject.
    Note: SR device studies must follow all the IDE regulations at 21 CFR 812, and must have an IDE application approved by FDA before they may proceed.
- 3.6. Non-significant risk device (NSRD) is a device that does not meet the definition of an SRD.
  Note: NSR device studies must follow the abbreviated requirements at 21 CFR 812.2(b). These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion. However, there is no need to make progress reports or final reports to FDA. NSR device studies do not have to have an IDE application approved by FDA.
  Note: FDA is the final arbiter as to whether a device study is SR or NSR and makes the determination when an IDE is submitted to FDA or if asked by the sponsor, clinical investigator, or IRB. See 21 CFR Â§ 812.2(b)(1).
- 3.7. Investigational New Device Exemption (IDE) is an application submitted to FDA to conduct a clinical investigation with an investigational device that is subject to 21 CFR 812.2 and is classified as an SRD. The IDE is submitted by the sponsor of the research. The FDA will provide a written authorization to conduct a clinical investigation within 30 days after receipt of the IDE. If the device is not an SRD, the investigation is considered by FDA to have an approved IDE unless FDA notifies the sponsor otherwise.
- 3.8. Marketed Device is a device approved by FDA for marketing and is generally in use for treatment or diagnostic purposes.
  Note: When a marketed device is used in a clinical investigation, it is subject to 21 CFR 812.2 unless it qualifies as an exempted investigation. IRB review and approval, however, is required.
- 3.9. Sponsor is the person who initiates, but does not actually conduct the investigation. The sponsor is responsible for complying with the requirements under FDA regulations at 21 CFR 812.40-47. The sponsor may be a device company, governmental agency, academic institution, private organization or an individual investigator.
- 3.10. Sponsor-Investigator is an individual that initiates and conducts an investigation, that is, under whose immediate direction the investigational device is administered, dispensed or used. An investigator who also serves as a sponsor must comply with all FDA requirements applicable to an investigator as well as a sponsor.
- 3.11. Treatment Use of an Investigational Device means use of a device that is not approved for marketing, but may be under clinical investigational, for a serious or immediately life-threatening disease or condition in patients for whom no comparable or satisfactory alternative device or other therapy is available. Under a treatment IDE, patients not in a clinical investigation may be treated utilizing the device in accordance with 21 CFR 812.36. IRB approval is required for treatment use of an investigational device.
- 3.12. Emergency Use means use of a test article on a human patient in a life-threatening or severely debilitating circumstance where no standard medically acceptable treatment is available and there is not sufficient time to obtain full IRB approval for use of the test article to treat the patient.
- 3.13. Unanticipated Adverse Device Effect (UADE) means an adverse effect caused by, or associated with, a device, if that effect was: 1) not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), and 2) the adverse effect relates to or impacts the rights, safety, or welfare of subjects.
- 3.14. A Custom Device (as defined in 21 CFR 812.3(b) and section 520(b) of the FFDA) means a device that meets all of the following criteria:
  It is necessarily different from generally available devices or performance standards to meet the order of an individual physician or dentist;
  (a) It is not generally available to, or used by, other physicians or dentists;
  (b) It is not generally available for purchase or dispensing upon prescription;
  (c) It is not offered for commercial distribution;
  (d) It is intended for use by an individual patient, or to meet the needs of the individual physician or dentist.

4.0 Requirements

- 4.1. All contracts between sponsors and UNMC, Nebraska Medicine, and BMC for investigational device studies must be reviewed and approved by UNMC Sponsored Programs Administration (SPA) or by UNeHealth, in compliance with HRPP policy 1.12 (Sponsored Research).
- 4.2. All contracts between sponsors and CHMC for investigational device studies must be reviewed and approved by UNMC Sponsored Programs Administration (SPA) or by UNeHealth, or by CHMC Administration, in compliance with HRPP policy 1.12 (Sponsored Research). If the contract is reviewed and approved by CHMC Administration it will also be reviewed by UNMC SPA or UNeHealth to assure the requirements of HRPP policy 1.12, section 4.3 are met.
- 4.3. Clinical investigations involving SR devices must be reviewed and approved by the full IRB in accordance with HRPP policy 2.2 (Full IRB Review). However, the IRB may determine select clinical investigations involving NSR devices and exempt devices that are no more than minimal risk may be eligible for expedited review in accordance with HRPP policy 2.3 (Expedited Review).
- 4.4. If the contract agreement requires compliance with ICH GCP, the IRB will review the submission in accordance with HRPP policy 1.13 (Compliance with ICH-GCP). The investigator will designate the need for ICH GCP compliance in the IRB application.
- 4.5. If a study involves an investigator-initiated IDE, it is the expectation of the Organization that the PI will also comply with the FDA-mandated sponsor requirements (21 CFR 812) and certify compliance by submitting Addendum P (Principal Investigator Responsibilities: Investigator-Initiated Device Trials) which specifies all of the responsibilities of the Sponsor-Investigator.
- 4.6. Any PI who has a study that is audited by the sponsor, a CRO or FDA must immediately notify the UNMC Chief Compliance Officer and provide the IRB with a copy of the report following the audit. When the study is audited by the Fred & Pamela Buffett Cancer Center Protocol Review Monitoring System (PRMS) Audit Committee, a copy of the report must be provided to the IRB.
- 4.7. If a study involves an investigator-initiated IDE, the PI must also comply with the FDA-mandated sponsor requirements.

5.0 IRB Procedures

- 5.1. The IRB will review information in the application to ensure that (1) the device has an IDE issued by the FDA, or satisfies the requirements for exemption from IDE; and (2) the device is not a banned device.
- 5.2. The IRB will review the information in the application to ensure that the PI has adequate controls in place for storage, security, and dispensing of investigational devices in accordance with 21 CFR 812.110. The IRB will assess whether:
  - 5.2.1. The device is stored and secured in a manner that restricts access to investigators. As appropriate this may be a cabinet that has a physical lock to which only an investigator has a key (physical or electronic), or some other equivalent process.
  - 5.2.2. The device is dispensed in a manner that assures that only subjects who have provided informed consent will be treated or tested/examined using the investigational device. This should involve marking the device in an easily visible manner that it is for investigational use only, and, as appropriate, include a mechanism to have a second party review the signed consent form prior to dispensing the device from a storage location, or some other equivalent process.
  - 5.2.3. The investigator and the departments, sections, or operating rooms where device is

used maintains records sufficient to document that the storage, security and dispensing of investigational devices has been in accordance with 21 CFR 812.110. These records may be physical or electronic, as long as they satisfy the requirements of 21 CFR 812.140, including, but limited to records of receipt, use or disposition of a device that relate to: (i) The type and quantity of the device, the dates of its receipt, and the batch number or code mark; (ii) The names of all persons who received, used, or disposed of each device, and (iii) Why and how many units of the device have been returned to the sponsor, repaired, or otherwise disposed of.

- 5.3. Unless the research is exempt from the FDA IDE regulations, the IRB will review the sponsor's determination of the risk classification of the device (SR or NSR) and make a determination of risk based upon the following:
  - 5.3.1. The potential harm associated with the device itself
  - 5.3.2. The proposed use of the device
  - 5.3.3. Any procedure necessary for implantation of the device
  - 5.3.4. A comparison of the risks of the device against the risks of alternative devices or procedures.
- 5.4. The IRBs determination of risk classification of the device and the rationale for the classification will be documented in the IRB minutes.
- 5.5. If the IRB has any question or concern about whether a study is SR and, therefore, requires an IDE, the PI will be instructed to contact the Food and Drug Administration (FDA) Center for Devices and Radiologic Health (CDRH) and obtain a written determination.
- 5.6. The IRB will notify the PI of the Board's SR/NSR determination. If the IRB disagrees with the sponsor or PI's determination that a device is NSR, the study can only be conducted within the Organization if an IDE is obtained. The PI is responsible for notifying the sponsor of the IRB's determination. The PI must provide the IRB with confirmation of this action.
  Note: In accordance with 21 CFR 812.150(b)(9), if the IRB determines that a device is SR and the sponsor had classified the device as NSR, the sponsor must submit to FDA a report of the IRB's determination within 5 work days after the sponsor first learns of the IRB determination. If FDA does not agree with the IRB's SR determination, the IRB will re-review the study. However, the IRB retains the ultimate authority in deciding whether or not to accept FDA's NSR classification.
- 5.7. NSR device studies do not require submission of an IDE application to the FDA before starting the study. The FDA considers an NSR device study to have an approved IDE application after obtaining and maintaining IRB approval. Sponsors and the PI must meet the abbreviated requirements at 21 CFR 812.2(b). These abbreviated requirements address labeling, IRB approval, informed consent, monitoring, records, reports, and prohibition against promotion.
- 5.8. If the IRB classifies a device as NSR, the IRB will continue to follow procedures in accordance with the IRB approval criteria HRPP policy 2.5 used in considering approval of any research involving an FDA-regulated product including all applicable local and regulatory requirements.
- 5.9. SR devices require submission of an IDE application to the FDA before starting the study. Final IRB approval and release of IDE studies is contingent upon the assigned IRB administrator's receipt of FDA notification approving the IDE. All protocol-related documents, including FDA notification, must contain matching IDE numbers.
- 5.10. For studies involving marketed SR devices for potential new indications, the IRB may require submission of an IDE application to the FDA upon consultation with both the sponsor and the FDA.
- 5.11. All unanticipated adverse device effects (UADEs) will be reported in accordance with HRPP policy 8.1 (IRB Review of Adverse Events and Adverse Device Effects).

6.0 Exemptions from IDE Requirements

- 6.1. Any of the following types of clinical investigations are exempt from IDE requirements (21

CFR 812.2(c)):

- 6.1.1. A clinical investigation with approved devices used in accordance with labeling. The device may have been approved for commercial distribution before May 28, 1976 or deemed substantially equivalent to a device commercially approved before May 28, 1976.
- 6.1.2. A clinical investigation with in vitro diagnostic devices, if the sponsor complies with applicable labelling requirements in 21 CFR 809.10(c) and if the testing:
  - 6.1.2.1. Is noninvasive; and
  - 6.1.2.2. Does not require an invasive sampling procedure that presents significant risk; and
  - 6.1.2.3. Does not by design or intention introduce energy into a subject; and
  - 6.1.2.4. Is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure.
- 6.1.3. A clinical investigation with a marketed device undergoing consumer preference testing, testing of a modification, or testing of a combination of two or more devices in commercial distribution, unless testing is for determining safety and efficacy and/or puts subjects at risk.
- 6.1.4. A custom device as defined in § 812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

- 6.2. Exemption from IDE regulations does not mean the study is exempt from IRB review and approval. If the study involves use of a device, whether or not the device has been approved by the FDA, the IRB's review and approval of the study must comply with all applicable local and federal regulations.

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6.3 Humanitarian Use Device (HUD)

1.0 Purpose

The purpose of this policy and procedure is to describe the Organization's requirements for the use of a medical device that has a Humanitarian Use Device (HUD) designation.

2.0 Policy

It is the policy of the Organization that all uses of an HUD will be reviewed and approved in accordance with FDA regulations at 21 CFR 50, 56 and 814 Subpart H, as well as HHS regulations at 45 CFR 46.

3.0 Definitions

- **3.1.** ***Humanitarian Use Devices (HUD):*** HUDs are intended to benefit patients by treating or diagnosing a disease or condition that affects not more than 8,000 individuals in the US per year. An HUD is a legally marketed device and is not investigational.
- **3.2.** ***Humanitarian Device Exemption (HDE):*** HDE is a Pre-Market Approval application which is exempt from the requirement of establishing a reasonable assurance of effectiveness. HDE approval is based upon, among other criteria, a determination by FDA that the HUD 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 while taking into account the probable risks and benefits of currently available devices or alternative forms of treatment.

4.0 IRB Review Procedures

- **4.1.** The use of a HUD after review and approval by the IRB does not constitute human subject research.
- **4.2.** The collection of safety and efficacy data about an HUD to support an application for a pre-marketing approval constitutes a clinical investigation subject to 21 CFR 50, 56.
  - **4.2.1.** If data can be collected in a clinical investigation for the HDE-approved indication no IDE is required. If data is being collected for a different indication than the HDE-approved indication, the clinical investigation requires an FDA-approved IDE.
  - **4.2.2.** If data is being collected in a clinical investigation for a different indication than the HDE-approved indication, then the IRB is required to make an SR/NSR determination (as required by 21 CFR 812.66). If the IRB, the sponsor or the FDA has made a SR determination then the clinical investigation requires an IDE.
- **4.3.** The convenved IRB will review and approve the use of an HUD before it is used within the organnization. Expedited review will not be used.
- **4.4.** The IRB will review the HUD application, which must include a summary of how the physician proposes to use the device, a description of any screening procedures, the HUD procedure, and any patient follow-up visits, tests or procedures; the consent form; and any additional materials supplied by the sponsor including the product labeling; and any patient information.
- **4.5.** The IRB will review the use of the HUD following the review criteria in 21 CFR 56.111.
- **4.6.** Once an HUD is reviewed and approved within the organization, subsequent use of the HUD does not require additional review.
- **4.7.** An HUD may be used outside its approved indication once it has been reviewed and approved within the organization.
- **4.8.** An HUD may be used in an emergency situation without prior IRB approval in accordance

with the applicable sections of HRPP policy 6.4 (Emergency Use of a Test Article).

- **4.9.** The UNMC IRB requires that written informed consent be obtained from patients who will be recipients of HUDs, except as described in section 4.10.
  - **4.9.1.** The Consent Form should include at least (1) 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; (2) a statement that effectiveness of this device for this use has not been demonstrated; (3) a description of any ancillary procedures associated with the use of the HUD; (4) a description of the use of the HUD; (5) all known risks or discomforts; (6) and an explanation of the postulated mechanism of action of the HUD in relation to the disease or condition.
  - **4.9.2.** If the HUD is being used outside its approved indication the Consent Form must be modified to state that the HUD is being used outside its approved indication (for example, "the device is safe and probably effective for X, but it is being used for Y …")
- **4.10.** Written informed consent is not required from patients who will be recipients of HUDs if all of the following conditions are met:
  - **4.10.1.** The patient is confronted by a life-threatening or severely debilitating situation necessitating the use of the test article.
  - **4.10.2.** Informed consent cannot be obtained from the patient because of an inability to communicate with, or obtain legally effective consent from the patient.
  - **4.10.3.** Time is not sufficient to obtain consent from the patient's LAR.
  - **4.10.4.** There is available no alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the patient's life.
- **4.11.** Continuing review of the use of the HUD is required no less often than annually. The Continuing Review application will be reviewed via expedited process (as per HRPP policy 2.3; Expedited Review).

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Revised: 5/26/2021 - Clarified requirement for IDE and for SR/NSR determination when conducting a clinical investigation with an HUD; clarified materials to be reviewed by the IRB; clarified that use of HUD off-label is allowable without additional review; described specific additional information to be included in the CF if HUD is used outside its approved indication; stylistic and organization changes

6.4 Emergency Use of a Test Article

1.0 Purpose

The purpose of this policy is to describe the requirements for utilization of a test article under emergency circumstances where there is not sufficient time to obtain IRB approval at a convened meeting.

2.0 Policy

It is the policy of the Organization that:

- 2.1. Emergency use of a test article (investigational drug, biologic, or device) must be conducted in full compliance with the requirements of FDA regulations at 21 CFR 56.102(d), 21 CFR 56.104(c).
- 2.2. In an emergency use situation, if time permits, the treating physician who is proposing to use the test article must obtain concurrence from the IRB Chair/designee through the Office of Regulatory Affairs (ORA) that the emergency use meets all FDA requirements.

3.0 Definitions

- 3.1. Emergency Use: The use of a test article on a human patient in a life-threatening or severely debilitating circumstance where no standard medically acceptable treatment is available and there is not sufficient time to obtain full IRB approval for use of the test article to treat the patient [21 CFR 56.102(d)].
  - 3.1.1. Life-threatening: Diseases or conditions where the likelihood of death is high unless the course of the disease is interrupted.
  - 3.1.2. Severely debilitating: Diseases or conditions that would likely cause major irreversible morbidity (e.g. loss of a limb, paralysis or stroke).
    Note: A life-threatening and/or severely debilitating condition does not necessarily mean that the condition is immediately life-threatening or may imminently result in death or irreversible morbidity. Rather, the patient must be in a situation requiring prompt administration of the test article before review at a convened meeting of the IRB is feasible and any treatment delay will have a significant deleterious effect on the patient. Consequently, premature death and/or persistent morbidity are likely.

4.0 General Considerations

- 4.1. Emergency Use of a test article (unapproved drug, device or biologic) does not constitute human subject research under HHS regulations. If the administration of the test article is subject to HHS regulations, the data related to such emergency use cannot be included in any report (for example, research article in a journal). However, Emergency use of a test article is considered a clinical investigation under FDA regulations, and data obtained during emergency use of the test article is subject to FDA inspection and may be required to be submitted to FDA in a marketing application.
- 4.2. Nothing in the policy is intended to limit the authority of a physician to provide emergency medical care, to the extent the physician is permitted to do so under applicable federal, state, or local law.
- 4.3. FDA allows physician requests for a single patient IND for compassionate or emergency use in accordance with 21 CFR 312.300. This is referred to as “expanded access use”. The patient or patients to be treated must have a serious or immediately life-threatening disease or condition and there is no comparable or satisfactory alternative therapy, but therapy is not emergent and there is sufficient time for prospective IRB review and approval. Expanded Access Use is subject to HRPP policy 6.5 (Expanded Access to Investigational Drugs and Devices for Treatment Use).
- 4.4. Emergency Use may be appropriate when an IND/IDE does not exist for the test article but there is reason to believe the patient would benefit, or when an IND/IDE exists and either there is no available clinical investigation, or the subject is not eligible for an available clinical investigation.

5.0 IRB Requirements

- 5.1. Physicians intending to use a test article under emergency circumstances should have carefully assessed the potential for therapeutic benefit to the patient and be assured that all of the following criteria are met:
  - 5.1.1. The test article has not been used at the Organization to date under the FDA emergency use provisions, except as noted in section 7.7 below.
  - 5.1.2. The patient is suffering from a life-threatening or severely debilitating condition.
  - 5.1.3. There is no available alternative method of approved or generally recognized therapy that provides an equal or greater likelihood of saving the patient’s life and/or alleviating a debilitating condition.
  - 5.1.4. When possible and/or required, the holder of the IND or IDE (sponsor or device developer) has authorized the emergency use.
  - 5.1.5. When the test article is a medical device, an independent assessment, as appropriate, has been obtained from an uninvolved physician that use of the test article is necessary.
  - 5.1.6. There is not sufficient time to obtain full IRB approval of a protocol.

6.0 FDA Notification

- 6.1. When there is an industry sponsor who is the holder of the IND/IDE, the sponsor will notify FDA as required.
- 6.2. When the investigator is the holder of the IND/IDE, the investigator will notify FDA as required.
- 6.3. When no IND/IDE exists, the treating physician will notify the drug/device developer who, in

turn, will notify FDA.

7.0 Procedures for Emergency Use of a Test Article

- 7.1. The treating physician must contact the Executive Chair/designee directly or thru ORA. The IRB Executive Chair/designee must concur that the proposed emergency use has met all the requirements of 21 CFR 56.102(d), 21 CFR 56.104(c), and the criteria in section 5.0 above.
- 7.2. The treating physician will complete section I of the Emergency Use of a Test Article Report and develop a consent form in RSS. The form documents information about the proposed emergency use.
- 7.3. The ORA will issue an acknowledgement that the use of the test article satisfies the requirements of 21 CFR 56.102(d)
- 7.4. If a test article is an investigational drug or biologic, and there is sufficient time, the treating physician must:
  - 7.4.1. Contact the Chair of the P&T Committee/designee and obtain a P&T emergency use approval.
  - 7.4.2. Notify the Executive Director of the Pharmacy or Investigational Drug Pharmacist of the emergency use, and provide information concerning financial responsibility for the pharmacy costs of the test article.
- 7.5. The treating physician must complete and submit section II of the Emergency Use of a Test Article Report thru RSS within five business days following initiation of the treatment. [21 CFR 56.104(c)].
- 7.6. The Emergency Use of a Test Article Report will be provided to the IRB as a notification at a convened IRB meeting.
- 7.7. Any subsequent use of the test article must have prospective IRB review and approval. *Note: FDA acknowledges that it would be inappropriate to deny emergency treatment to a second individual if the only obstacle is the IRB has not had sufficient time to convene a meeting to review a protocol (reference "1998 FDA Information Sheets").*
- 7.8. If the physician decides not to use the test article the ORA must be promptly notified.

8.0 Informed Consent

- 8.1. The treating physician should be prepared to obtain written informed consent from the patient or the patient's legally authorized representative (LAR) unless conditions in section 8.4 below are met.
- 8.2. The Informed Consent Form (ICF) is generated in RSS based on a modified template as below.
  - 8.2.1. The ICF must comply with the requirements of 21 CFR 50.25 (Basic and Additional Elements of Consent) and HRPP policy 5.1 (Obtaining Informed Consent from Research Subjects), section 4.1 (Basic Elements of Informed Consent).
  - 8.2.2. The elements of informed consent should be worded to reflect the nature of the emergency situation (that is, the patient is being treated for a life-threatening or severely debilitating condition and there are no alternative therapeutic methods that provide an equal or greater likelihood of saving the patient's life).
  - 8.2.3. The ICF must include HIPAA required information and a clear disclosure of the financial obligations of the patient.
- 8.3. Informed consent is not required if both the treating physician and a physician who is not

otherwise participating in use of the agent certify in writing all of the following [21 CFR 50.23(a)]:
    - 8.3.1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
    - 8.3.2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
    - 8.3.3. Time is not sufficient to obtain consent from the subject's legal representative.
    - 8.3.4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.
      Note: The IRB Executive Chair/designee can provide the required certification if they are not participating in any clinical investigation involving the test article. Alternatively, another independent physician can provide certification.
- 8.4. If time is not sufficient to obtain the independent physician determination before use of the test article, the actions of the investigator must be reviewed and evaluated in writing by an independent physician within 5-6 working days. The IRB must be notified within 5 working days when an emergency waiver is used. This notification must not be construed as an approval for the emergency waiver by the IRB. The IRB Executive Chair/designee will review the report to verify that circumstances of the emergency waiver conformed to FDA regulations.

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Revised: 12/7/2022 - Deleted description of expanded access and referred instead to HRPP Policy 6.5; revised procedures to reflect modified “Emergency Use of a Test Article Report” in RSS (including sequential completion of sections I and II of the report); clarified that IRB notification will be made at a convened meeting. {Approved Chris Kratochvil (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

Board notified: 1/16/2023

Revised 1/22/2024 – revised section 4.1 to specify “test article (unapproved drug, device or biologic)” rather than just drug or biologic; minor stylistic changes. {Approved Russell McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

6.5 Expanded Access to Investigational Drugs and Devices for Treatment Use

1.0 Purpose

- **1.1.** The purpose of this policy and procedure is to describe the requirements for utilization of an investigational drug or device (test article) for treatment use. This applies to expanded access for individuals or groups of patients with serious or immediately life- threatening diseases or conditions who lack therapeutic alternatives (compassionate use).
- **1.2.** Emergency use of a test article on a human patient in a life-threatening or severely debilitating circumstance where no standard medically acceptable treatment is available and where there is not sufficient time to obtain IRB approval at a convened meeting is addressed in HRPP Policy 6.4 (Emergency Use of a Test Article).

2.0 Policy

- **2.1.** It is the policy of the Organization that expanded access to investigational drugs and devices for individuals or groups of patients with serious or immediately life- threatening diseases or conditions who lack therapeutic alternatives (compassionate use) must be conducted in full compliance with the requirements of FDA regulations at 21 CFR 312 subpart I.

3.0 Definitions

- **3.1.** Expanded Access: Expanded access refers to the treatment use of an investigational drug or device for patients with serious or immediately life-threatening diseases who lack therapeutic alternatives
  - **3.1.1.** Expanded access may also refer to (1) use in situations when a drug has been withdrawn for safety reasons, but there exists a patient population for whom the benefits of the withdrawn drug continue to outweigh the risks; (2) use of a similar, but unapproved drug (e.g., foreign-approved drug product) to provide treatment during a drug shortage of the approved drug; (3) use of an approved drug where availability is limited by a risk evaluation and mitigation strategy (REMS) for diagnostic, monitoring, or treatment purposes, by patients who cannot obtain the drug under the REMS.
  - **3.1.2.** The primary purpose of the expanded access use is to diagnose, monitor, or treat a patient's disease or condition rather than to obtain the kind of information about the drug that is generally derived from clinical trials. The terms expanded access, treatment use, and compassionate use may be used interchangeably.
- **3.2.** Immediately life-threatening disease or condition: a stage of disease in which there is reasonable likelihood that death will occur within a matter of months or in which premature death is likely without early treatment.
- **3.3.** Serious disease or condition: a disease or condition associated with morbidity that has substantial impact on day-to-day functioning. Short-lived and self-limiting morbidity will usually not be sufficient, but the morbidity need not be irreversible, provided it is persistent or recurrent. Whether a disease or condition is serious is a matter of clinical judgment, based on its impact on such factors as survival, day-to-day functioning, or the likelihood that the disease, if left untreated, will progress from a less severe condition to a more serious one (21 CFR 312.300(b)).
- **3.4.** Intermediate size population: refers to a group of patients generally fewer than are treated under a typical treatment IND or protocol. FDA regulations do not impose specific numerical limitations for when an intermediate size patient population expanded access IND or protocol (as opposed to a treatment IND or protocol) may be appropriate.
- **3.5.** Treatment IND/IDE: refers to a mechanism for providing eligible subjects with investigational drugs or devices for the treatment of serious and life-threatening illnesses for which there are no

satisfactory alternative treatments. A treatment IND/IDE may be granted by FDA after sufficient data have been collected to show that the investigational drug or device may be effective and does not have unreasonable risks. Because data related to safety and side effects are collected, treatment IND/IDEs also serve to expand the body of knowledge about the article [21 CFR 312.34 and 21 CFR 812.36].

4.0 General Considerations

- **4.1.** Except as described below, use of an investigational drug or device (test article) for treatment under expanded access requires review and approval by the convened IRB before treatment with the investigational drug may begin (21 CFR 312.305(c)(4)).
- **4.2.** Individual patient expanded access may proceed without IRB approval provided:
  - **4.2.1.** The physician submitting an individual patient expanded access requests waiver of convened IRB review under 21 CFR 56.105 by checking box 10b on FDA form 3926; and
  - **4.2.2.** The physician submitting an individual patient expanded access requests and obtains concurrence by the IRB chairperson or another designated IRB member before treatment use begins.
- **4.3.** Expanded access to an investigational drug or device for treatment use requires informed consent as described in 21 CFR Part 50, unless one of the exceptions found in Part 50 applies.
- **4.4.** Individual patient expanded access is generally limited to a single course of therapy for a specified duration (21 CFR 312.310(c)(1)). However, the FDA may authorize multiple courses of therapy or chronic therapy for individual patient expanded access, including authorizing individual patient expanded access to treat a chronic disease or condition that requires extended treatment (as reflected in 21 CFR 312.310(c)(1))
- **4.6.** Emergency use of a test article as described in HRPP Policy 6.4 may proceed without IRB approval provided conditions described in that policy are satisfied.

5.0 Investigator procedures

- **5.1.** Physicians intending to use an investigational drug or device for treatment of a **single patient** must:
  - **5.1.1.** Determine that the probable risk to the patient from the investigational drug is not greater than the probable risk from the disease or condition (21 CFR 312.310(a)(1))
  - **5.1.2.** Complete and submit to the IRB the Application for Single Patient Expanded Access thru RSS.
  - **5.1.3.** Submit to the IRB a copy of the completed FDA Form 3926.
  - **5.1.4.** Submit written permission from the holder of the IND or IDE to use the investigational drug or device.
  - **5.1.5.** Submit consent form (and information sheet as appropriate) for use by single patient.
- **5.2.** Protocols for expanded access for **intermediate-size patient populations** (21 CFR 312.315) and expanded access for widespread treatment use through a **treatment IND or treatment protocol** (21 CFR 312.320) must be submitted on the Biomedical Application thru RSS.
- **5.3.** If the physician intending to use the test article submits the expanded access IND or protocol to the FDA he/she is considered a sponsor, and must comply with the responsibilities for sponsors set forth in 21 CFR 312.305(c)(5).

6.0. IRB / ORA procedures

- **6.1.** When the ORA is contacted by a physician intending to use the test article for single patient expanded access, the IRB Administrator will document the call, obtain pertinent information about the proposed single patient Expanded Access use, notify the IRB Executive Chair, and instruct the treating physician to complete and submit the Single Patient Expanded Access application thru RSS and to contact the IRB Executive Chair/designee.
- **6.2.** The IRB application for Single Patient Expanded Access must be reviewed and approved by the convened IRB except when the physician submitting an individual patient expanded access IND requests waiver of convened IRB review under 21 CFR 56.105 (by checking box

10b on FDA form 3926).

- **6.3.** The Biomedical application for expanded access for an intermediate size population or for Treatment IND/IDE must be reviewed and approved by the convened IRB.
- **6.4.** The convened IRB must review the application and request using the criteria described in 21 CFR 56.111. *Recognizing that the purpose is treatment, the IRB should interpret the criteria appropriately.* The board should:
  - **6.4.1.** Consider whether the safety information is reasonable in relationship to the anticipated benefit from the treatment plan;
  - **6.4.2.** Ensure risks are minimized to the extent possible in the proposed treatment plan;
  - **6.4.3.** Determine that there are adequate provisions for ensuring the safety of the patient, including adequate monitoring and appropriate plans for collecting and reporting the data;
  - **6.4.4.** Confirm that HIPAA requirements will be followed to ensure confidentiality of the medical record;
  - **6.4.5.** Confirm that the treating physician will follow standard medical practice to protect the privacy interests of the patient;
  - **6.4.6.** When the patient is likely to be vulnerable to coercion or undue influence additional safeguards are included in the treatment plan to protect the rights and welfare of the patient;
  - **6.4.7.** When the patient is a child, confirm the provisions of 21 CFR 50.52 are met; and
  - **6.4.8.** Review and approve an informed consent document and process that is appropriate to the treatment use (see section 7.2).
- **6.5.** If a physician submitting an individual patient expanded access IND requests waiver of convened IRB review under 21 CFR 56.105 by checking box 10b on FDA form 3926, the IRB application for Single Patient Expanded Access Program application must be reviewed by the IRB Executive Chair or IRB Chair/VC or designee.
  - **6.5.1.** The IRB Executive Chair or IRB Chair/VC or designee may determine concurrence utilizing the criteria described in section 6.4.

7.0 Informed Consent

- **7.1.** Written informed consent must be obtained from the patient or patient's legally authorized representative (LAR) in accordance with provisions of 21 CFR 50.25 and HRPP Policy 5.1 (Obtaining Informed Consent from Research Subjects).
- **7.2.** Given the treatment nature of the use, consent documents should meet the requirements listed in 21 CFR 50.25, using plain language that is specifically aimed at "patients" who expect direct benefit, as opposed to "subjects" who may not expect direct benefit.
- **7.3.** The ICF must include HIPAA required information and a clear disclosure of the financial obligations of the patient.

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