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).

DOCUMENT HISTORY:

Written: 1/25/2016 (Approved: 1/25/2016) - original author not recorded

Revised: 3/2/2018 - revision not documented

Revised 1/24/2024 - add reference to FDA 30-day rule (section 5.1.1); added IND exemption 4 (section 6.4). {Approved Rusty McCulloh (Institutional Official), Bruce Gordon (Assistant Vice Chancellor for Regulatory Affairs, Executive Chair)}

Revision #6
Created Thu, Oct 24, 2019 9:40 PM by Autumn M Eberly
Updated Wed, Jan 31, 2024 5:07 PM by Robert A Lewis