Investigational Drugs or Biologics Used in Research

Introduction:
The use of an Investigational Drug and/or Biologic in research is subject to the United States Code of Federal Regulations Title 21 - Food & Drugs Part 312 - Investigational New Drug Application (IND). This policy defines the applicability of the Code of Federal Regulations and the procedures the UHCMC IRB follows to determine whether an IND is needed for a clinical investigation; outlines the responsibilities of the investigator who holds the IND and establishes procedures for the proper control, storage, use and handling of investigational drugs.

Definitions:
Research: As defined by Department of Health and Human Services (DHHS), any systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

Under FDA regulations activities are “research” when they involve:

a. Use of a drug other than the use of an approved drug in the course of medical practice (21 CFR 312.3 (b)).

b. Use of a medical device other than the use of an approved (means approved by the FDA for marketing) medical device in the course of medical practice (Food, Drug and Cosmetic Act 530 (g) (3) (a) (i)).

Investigational New Drug: A new drug or biological drug that is used in a clinical investigation. The term also includes a biological product that is used in vitro for diagnostic purposes. The terms “investigational drug” and “investigational new drug” are deemed to be synonymous for purposes of this part. 21CFR 312.3

Drug Dispensation: The term dispense means the final association of a drug with a particular patient pursuant to the prescription, drug order, or other lawful order of a prescriber and the professional judgment of and the responsibility for: interpreting, preparing, compounding, labeling, and packaging a specific drug. (Ohio Rule 4729-5-01)

Drug Used in Clinical Investigation: Any drug, biological, botanical or other substance used specifically for a clinical investigation as described in the investigational protocol. Such drugs shall be either commercially available or not commercially available and used according to, or outside of, FDA-approved indications.

Investigational Drug Services (IDS): Refers to the UH pharmacy responsible for the storage and dispensation of investigational drugs.

Sponsor: Means a person who takes responsibility for and initiates a clinical investigation. The sponsor may be an individual or pharmaceutical company, governmental agency, academic institution, private organization, or other organization. The sponsor does not actually conduct the investigation unless the sponsor is a sponsor-investigator.

UHCMC IRB Policies and Procedures
Sponsor-Investigator: Means an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. The term does not include any person other than an individual. The obligations of a sponsor-investigator include both those of a sponsor and those of an investigator. A sponsor-investigator of an IND at University Hospitals cannot be a fellow or a resident.

Policy:
The Clinical Research Center, Regulatory/FDA Guidance Core and the IRB Administrative Office will work with the investigator and manufacturer to determine the need for an Investigational New Drug Application. The proposed research is not allowed to begin until a valid IND is in effect, or until it has been determined by the IRB or FDA that the research meets exemptions from the requirement for an Investigational New Drug Application under 21 CFR 312.2(b). This includes recruiting, obtaining consent, and screening participants for a specific study that is subject to the IND.

In order to verify the validity of the IND, the IRB Administrative Office requires that a copy of the letter from the FDA with the IND assignment for the clinical investigation under review or a letter from the FDA stating that an IND is not needed, be submitted to the IRB with the new protocol application.

In accordance with FDA regulations 21 CFR 312.3, and Good Clinical Practice (GCP) guidelines, the requirements applicable to a sponsor-investigator under part 312 include both those of an investigator and a sponsor. The responsibilities include the following:

- Maintaining the Investigational New Drug application
- Obtaining Qualified Investigators and Monitors
- Providing Necessary Information and Training for Investigators
- Monitoring the Investigation
- Controlling the Investigational Agent
- Reporting Significant Adverse Events to FDA/Investigators
- Maintaining and Retaining Accurate Records
- Implementing and maintaining quality assurance with written Standard Operating Procedures (SOP’s)

When a UHCMC Investigator is the sponsor of the Investigational New Drug (sponsor-investigator), the UHCMC IRB requires the investigator to meet with a representative of the Regulatory/FDA Guidance Core to review his/her FDA responsibilities as a sponsor-investigator. In addition, the sponsor-investigator must complete the University Hospitals Clinical Research Center investigator training modules.

If the investigator indicates on their application that there is no Investigational New Drug number, the IRB will be responsible for determining whether an Investigational New Drug Application is required in accordance with the following criteria:

In accordance with FDA regulations 21 CFR 312.2 all clinical investigations that involve drugs (any use of a drug other than the use of a marketed drug in the course of medical practice must have an Investigational New Drug Application, unless the drug meets one of the exemptions from the requirement for an Investigational New Drug Application in 21 CFR 312.2(b).

UHCMC IRB Policies and Procedures
These categories are:

**Exemption #1:**
- The drug is lawfully marketed in the United States.
- The investigation is not intended to be reported to FDA as a well-controlled study in support of a new indication for use nor intended to be used to support any other significant change in the labeling for the drug;
- The investigation is not intended to support a significant change in the advertising for the product.
- 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 product.
- The investigation is conducted in compliance with the requirements for institutional review set forth in part 56 and with the requirements for informed consent set forth in part 50.
- The investigation is conducted in compliance with the requirements of 21 CFR 312.7.
- The research does not involve an exception from informed consent under 21 CFR 50.24.

**Exemption #2:**
The research involves one of the following *in vitro* diagnostic biological product:
- Blood grouping serum;
- Reagent red blood cells; and
- Anti-human globulin.
- The *in vitro* diagnostic biological product is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure.
- The *in vitro* diagnostic biological product is shipped in compliance with 21 CFR 312.160.
- The research does not involve an exception from informed consent under 21 CFR 50.24.

**Exemption #3:**
- The drug is intended solely for tests in vitro or in laboratory research animals.
- The drug is shipped in compliance with 21 CFR 312.160.
- The research does not involve an exception from informed consent under 21 CFR 50.24.

**Exemption #4:**
- Use of a placebo.
- The research does not involve an exception from consent under 21 CFR 50.24.

In accordance with FDA regulations 21 CFR 312 and UHCMC policies, the Sponsors and/or Investigators are responsible for the proper ordering, handling, storage and disposition of investigational drugs in clinical trials at UHCMC. If the Principal Investigator does not delegate this responsibility to UHCMC UHCMC IRB Policies and Procedures.
Investigational Drug Services, then the Principal Investigator must complete an Investigational Drug Services Exception request form and ensure the following:

1. Prescribing
   1.1 Prescribing an investigational drug must be done by an authorized prescriber listed on the IRB approved protocol. The authorized prescriber must be licensed and be credentialed through UH.

2. Procurement
   2.1. Procurement of an investigational drug must be done by the Principal Investigator or designated study personnel according to the terms of the executed agreement and only after the protocol has been approved by the IRB.

3. Receipt
   3.1. Investigational drugs may only be received by the Principal Investigator or designated study personnel at a UHCMC business address (the address listed on the 1572).
   
   3.2. Upon receipt of the investigational drug, the Principal Investigator or designee will inventory the shipment to ensure that the information on the packing slip matches exactly with what has been shipped, including lot numbers and quantity.
   
   3.3. Packing slips and documentation of inventory must be maintained with the study records.

4. Storage/Labeling
   4.1. Investigational drugs used in conjunction with a research protocol must be kept in a locked and secured area and must be labeled “Caution: New Drug-Limited by Federal Law (or United States) Law to Investigational Use.”
   
   4.2. Additional labeling for inpatient Investigational Drugs shall be in compliance with UHHS policies. Any other information pertinent to administration of the Investigational Drug may also be included on the label (e.g. expiration date).
   
   4.3. Labeling for outpatient Investigational Drugs must include: subject study identification number, date dispensed, and prescription number, study drug name, directions for use, the name of the principal investigator, the name and address of prescriber and quantity dispensed.
   
   4.4. Access to investigational drugs must be limited to personnel designated by the Principal Investigator.

5. Dispensing
   5.1. The investigational drug may not be given to anyone not enrolled in the study.
   
   5.2. The Principal Investigator must not supply the investigational drug to any person not authorized.
5.3. Dispensing of the study drug must be done by an authorized prescriber listed on the IRB approved protocol.

5.4. For accountability purposes an investigational drug accountability log(s) must be kept for all investigational drug studies. Documentation of the following elements should be recorded for each drug used:

- Name of Principal Investigator
- Name of Study Drug
- Protocol title
- Drug dose, form and strength
- Expiration date of the drug (if available)
- Research subject study ID number
- Date dispensed
- Quantity Dispensed
- Dose
- Date returned
- Quantity returned
- Balance
- Lot #
- Signature and/or initials of staff member

5.5. Personnel may not remove any drug(s) from the standard drug inventory and substitute them for an investigational drug, even if the drug, under study, is approved and used in practice.

6. Maintaining a Drug Accountability Log:

6.1. Investigational drug logs must be maintained with the study’s regulatory records for the period of time required by the federal regulations or terms of the agreement, whichever is longer.

6.2. The full names, titles/positions, signatures and/or initials of all UHCMC personnel responsible for maintaining or documenting in the log(s) must be indicated on either a cover sheet or in the log itself.

6.3. The Principal investigator or designated study personnel must regularly review the drug logs to ensure that there is an adequate amount of drugs available to conduct the study procedures.

6.4. Drug records must show the receipt, shipment, or other disposition of the investigational drug in compliance with UH Policy MM-4 “Investigational Drugs”.

6.5. The disposition of the drug, including dates, quantity and use by research subjects must be recorded.

7. Disposition

7.1. Upon conclusion or termination of the clinical investigation, or by the sponsor’s request, the principal investigator shall return to the sponsor any remaining supply of the investigational drug or otherwise dispose of the drug as the sponsor directs. The investigational drug should not be disposed of
by the principal investigator or study personnel without obtaining advanced written permission from the sponsor.

7.2. Documentation of why, when, and the personnel involved is required.

**REFERENCES:**

21 CFR 50
21 CFR 60
21 CFR 312
Guideline for Good Clinical Practice
Ohio Rule 4729-5-01

**Related Policies:**

IRB Policy, Investigator Responsibilities
UH Policy: MM-4 Investigational Drugs
UHCMC Investigational Drug Services Exemption Request