I. PURPOSE

The purpose of this SOP is to delineate when an investigator must obtain an Investigational New Drug (IND) or Investigational Device Exemption (IDE) Submission prior to IRB approval of proposed research.

II. POLICY STATEMENT

The U.S. Food and Drug Administration (FDA) regulates the marketing of new drugs, biologics and devices. FDA's regulations specify the circumstances under which either an IND (21 CFR 312, 361) or an IDE (21 CFR 812) are required prior to conducting a clinical investigation. When a marketed drug, radioisotope, cold isotope or device is the subject of proposed research, investigators are required to submit their determination that the research meets the requirements for exemption from these requirements. They must also submit supporting documentation to allow the IRB to concur or disagree with their determination that an IND or IDE is not required for that use. If uncertainty exists, the IRB may resolve the matter by requesting that the investigator consult with FDA.

III. SCOPE

These policies and procedures apply to all investigators, IRB members and IRB staff.

IV. DEFINITIONS

Humanitarian Device Exemption (HDE): A marketing application for an HUD (Section 520(m) of the Federal Food, Drug, and Cosmetic Act (FD&C Act)). An HDE is exempt from the effectiveness requirements of Sections 514 and 515 of the FD&C Act and is subject to certain profit and use restrictions. An approved HDE authorizes marketing of a Humanitarian Use Device (HUD).

Humanitarian Use Device: A medical device intended to benefit patients in the treatment or diagnosis of a disease or condition that affects or is manifested in not more than 8,000 individuals in the United States per year.

IND: An Investigational New Drug Application (IND) is a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans. Such authorization must be secured prior to interstate shipment and administration of any new drug or biological product that is not the subject of an approved New Drug Application or Biologics/Product License Application.

Investigational Device Exemption (IDE): IDE refers to the regulations under 21 CFR 812. An approved IDE means that the IRB (and FDA for significant risk devices) has approved the sponsor's study application and all the requirements under 21 CFR 812 are met. An investigational device exemption (IDE) allows the investigational device to be used in a clinical study in order to collect safety and effectiveness data. An approved IDE permits a device to be shipped lawfully for the purpose of conducting investigations of

the device without complying with other requirements of the Food, Drug, and Cosmetic Act (FD&C Act) that would apply to devices in commercial distribution.

Investigational New Drug: Investigational new drug means 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 policy.

Investigational Device: A device, including a transitional device, that is the object of an investigation (i.e., a clinical investigation or research involving one or more subjects to determine the safety or effectiveness of a device).

Medical Device: An instrument, apparatus, implement, machine, contrivance, implant, in vitro reagent, or other similar or related article, including a component, part, or accessory, which is recognized in the official National Formulary, or the United States (U.S.) Pharmacopoeia, and intended for use in the diagnosis of disease or other conditions, or in the cure, mitigation, treatment, or prevention of disease, in man, or intended to affect the structure or any function of the body of man, and which does not achieve any of its primary intended purposes through chemical action within or on the body of man and which is not dependent upon being metabolized for the achievement of any of its primary intended purposes.

Radioactive Drug: Any substance defined as a drug in section 201(g)(1) of the Federal Food, Drug, and Cosmetic Act which exhibits spontaneous disintegration of unstable nuclei with the emission of nuclear particles or photons and includes any nonradioactive reagent kit or nuclide generator which is intended to be used in the preparation of any such substance but does not include drugs such as carbon-containing compounds or potassium-containing salts which contain trace quantities of naturally occurring radionuclides.

Significant Risk Device: An investigational device that is (1) intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject; (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; (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 (4) otherwise presents a potential for serious risk to the health, safety, or welfare of a subject. (21 CFR 812.3(m)).

V. PROCEDURES

A. Investigational New Drug

When use of an investigational drug is proposed, an IND Submission to the FDA is required. Confirmation of the FDA-distributed IND number is required for final IRB approval or in the case of single patient treatment INDs, concurrence to be issued.

The IRB will confirm the validity of the IND number by requiring that the investigator submit the notification of the IND number assigned from the FDA, a letter from the sponsor, or the commercially or NIH-sponsored protocol containing the IND number.

B. Research Involving an FDA-Approved Drug for an Unapproved Use

The clinical investigation of a drug product that is lawfully marketed in the United States does not require submission of an IND provided that one of the following Exemptions is met:

1. §312.2(b) Exemption 1: All five conditions specified in 21 CFR 312.2(b)(1) are met:
    - (a) 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;
    - (b) If the drug that is undergoing investigation is lawfully marketed as a prescription drug product, the investigation is not intended to support a significant change in the advertising for the product;
    - (c) 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;
    - (d) The investigation is conducted in compliance with the requirements for IRB review and informed consent [21 CFR parts 56 and 50, respectively]; and
    - (e) The investigation is conducted in compliance with the requirements concerning the promotion and sale of drugs [21 CFR 312.7].
2. §312.2(b) Exemption 2:
    - (a) A clinical investigation is for an in vitro diagnostic biological product that involves one or more of the following:
        - (1) Blood grouping serum
        - (2) Reagent red blood cells
        - (3) Anti-human globulin
    - (b) The diagnostic test is intended to be used in a diagnostic procedure that confirms the diagnosis made by another, medically established, diagnostic product or procedure; and

(c) The diagnostic test is shipped in compliance with 21 CFR 312.160.

3. §312.2(b) Exemption 5: A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND.
4. §312.2(b)(6): A clinical investigation involving an exception from informed consent under § 50.24 of this chapter is not exempt from the requirements of this part.

C. Research Involving Radioactive or Cold Isotopes

1. Radioactive Drug or Biological Product (§361.1)

   Human research using a radioactive drug or biological product may be conducted without an IND if:

   (a) It involves basic research not intended for immediate therapeutic, diagnostic, or similar purposes, or otherwise to determine the safety and efficacy of the product;
   (b) The use in humans is approved by a Radioactive Drug Research Committee (RDRC) that is composed and approved by FDA;
   (c) The dose to be administered is known not to cause any clinically detectable pharmacological effect in humans, and
   (d) The total amount of radiation to be administered as part of the study is the smallest radiation dose practical to perform the study without jeopardizing the benefits of the study and is within specified limits.

2. Clinical Investigations Using Cold Isotopes of Unapproved Drugs

   As there is no specific regulation analogous to 21 CFR 361.1 that addresses cold isotopes of approved drugs and unapproved drugs when used for basic research purposes, the IRB follows the FDA guidance (Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND). In exercising its enforcement discretion, FDA does not intend to object to clinical investigations using cold isotopes of unapproved drugs being conducted without an IND, provided the following conditions are met (the conditions are based on the criteria for studies using radiolabeled drugs (see 21 CFR 361.1):

   (a) The research is intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a drug labeled with a cold isotope or regarding human physiology, pathophysiology, or biochemistry;
   (b) The research is not intended for immediate therapeutic, diagnostic, or preventive benefit to the study subject;

(c) The dose to be administered is known not to cause any clinically detectable pharmacologic effect in humans based on clinical data from published literature or other valid human studies;
(d) The quality of the cold isotope meets relevant quality standards; and
(e) The investigation is conducted in compliance with the requirements for review by an IRB (21 CFR part 56) and the requirements for informed consent (21 CFR part 50).

D. Investigator's Responsibilities

The FDA's Guidance assigns the responsibility to the investigator to ensure that the above requirements are met.

1. The IRB will review the information provided by the investigator.
2. If the IRB concurs with the investigator's determination, then an IND is not required.
3. If the IRB does not concur, the investigator must either submit a request for an exemption from the FDA or obtain an IND.
   (a) If the FDA issues an exemption, an IND is not required.
   (b) If the FDA disagrees that the investigation meets the criteria for exemption, the investigator must obtain an IND for the proposed investigational use of the drug/biologic.

E. Investigational Devices

The Investigational Device Exemptions (IDE) regulations (21 CFR 812) describe three types of device studies: significant risk (SR), non-significant risk (NSR), and exempt studies. Sponsors are responsible for making the initial risk determination and should provide the IRB with their risk assessment and the rationale used in making its SR or NSR determination.

The IRB will confirm the validity of the IDE number by requiring that the investigator submit the notification of the IDE number assigned from the FDA, a letter from the sponsor, or the commercially or NIH-sponsored protocol containing the IDE number.

1. Significant Risk Devices
   (a) If the Sponsor or the FDA has already determined that the device is a significant risk device, the investigator must present evidence of an FDA-approved IDE.
2. Non-Significant Risk Devices
   (a) An IDE is not required prior to IRB review and/or approval of a study of a NSR device, however the IRB must make a determination that the device

is an NSR device.

(1) In order to make a determination, the IRB will review the relevant information provided by the sponsor and investigator at a convened meeting. The required information includes a description of the device, reports of prior investigations conducted with the device, the proposed investigational plan, and subject selection criteria.

(2) The IRB may agree or disagree with the sponsor's initial NSR determination.

(b) If the IRB determines the device is NSR, the IRB may approve the study using the criteria at 21 CFR 56.111. The study may begin without submission of an IDE application to FDA. The approved NSR device must comply with the abbreviated IDE requirements defined below:

(1) The device is not a banned device.

(2) The sponsor labels the device in accordance with 21 CFR §812.5.

(3) The sponsor obtains IRB approval of the investigation after presenting the reviewing IRB with a brief explanation of why the device is not a significant risk device and maintains such approval.

(4) The sponsor ensures that each investigator participating in an investigation of the device obtains, from each subject under the investigator's care, consent under 21 CFR §50 and documents it, unless documentation is waived.

(5) The sponsor complies with the requirements of 21 CFR §812.46 with respect to monitoring investigations;

(6) The sponsor maintains the records required under 21 CFR §812.140(b) (4) and (5) and makes the reports required under 21 CFR §812.150(b) (1) through (3) and (5) through (10);

(7) The sponsor ensures that participating investigators maintain the records required by 21 CFR §812.140(a)(3)(i) and make the reports required under §812.150(a) (1), (2), (5), and (7); and

(8) The sponsor complies with the prohibitions in 21 CFR §812.7 against promotion and other practices.

(c) If an IRB determines that an investigation, presented for approval under 812.2(b)(1)(ii), involves a significant risk device, it shall so notify the investigator and, where appropriate, the sponsor. The study may not be approved until the investigator presents evidence of an FDA-approved IDE or the FDA makes a final determination that the device is NSR.

3. Humanitarian Use Devices

   (a) The investigator must provide evidence of FDA-approved HDE prior to IRB approval of HUD studies.

   (b) All reviews for uses of a HUD will be conducted in accordance with IRB SOP 412.

4. Devices that Qualify for an Exemption

In accordance with 21 CFR 812.2(b), sponsors and investigators of certain studies are exempt from the requirements of 21 CFR Part 812 (with the exception of §812.119, disqualification of a clinical investigator). Examples of exempt studies are consumer preference testing, testing of a device modification, or testing of two or more devices in commercial distribution if the testing does not collect safety or effectiveness data, or put subjects at risk. These studies include:

(a) Studies of an already cleared medical device in which the device is used or investigated in accordance with the indications in the cleared labeling are exempt from Part 812.

(1) Studies of a cleared device *for a new use* must comply with the human subject protection (informed consent and additional safeguards for children in research), IRB, and IDE regulations.

(2) Studies of a PMA approved device are exempt from the IDE requirements if the device is being studied for the indications in the approved labeling.

(b) Diagnostic device studies (e.g., *in vitro* diagnostic studies) are exempt from the requirements of 21 CFR Part 812 under certain circumstances.

(1) If the sponsor complies with the requirements at 21 CFR 809.10(c) for labeling; and

(2) If the testing: (i) is noninvasive; (ii) does not require an invasive sampling procedure that presents significant risk; (iii) does not by design or intention introduce energy into a subject; and (iv) is not used as a diagnostic procedure without confirmation of the diagnosis by another, medically established diagnostic product or procedure (21 CFR 812.2(c)(3)).

(c) A custom device, as defined in 21 CFR §812.3(b), unless the device is being used to determine safety or effectiveness for commercial distribution.

F. Medical Device Committee Approval

In accordance with CHOP Hospital Policy, the approval of the Medical Device Committee is required for all devices not approved for clinical use at CHOP. Documentation of review and approval is required prior to final IRB approval.

VI. APPLICABLE REGULATIONS AND GUIDELINES

45 CFR 46.108, 45 CFR 46.111	21 CFR 312, 21 CFR 314.21
21 CFR 56.108, 21 CFR 56.111	21 CFR 812
Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND (CDER, CBER, CFSAN, September 2013)	IND Exemptions for Studies of Lawfully Marketed Drug or Biological Products for the Treatment of Cancer (CDER, CBER, January 2004)
Expanded Access to Investigational Drugs for Treatment Use —Questions and Answers (CDER, CBER, June 2016, updated October 2017)	Individual Patient Expanded Access Applications: Form FDA 3926 (CDER, CBER, June 2016, updated October 2017)
Guidance for Industry and Food and Drug Administration Staff; Humanitarian Use Device (HUD) Designations (CDRH, September 2019)	Guidance for Industry and Food and Drug Administration Staff; Humanitarian Device Exemption (HDE) Program (CDRH, September 2019)
FDA Decisions for Investigational Device Exemption Clinical Investigations (CDRH, August 2014)	Guidance for Industry and Researchers; The Radioactive Drug Research Committee: Human Research Without An Investigational New Drug Application (CDHR, CBER, August 2010)
Information Sheet Guidance for IRB's, Clinical Investigators and Sponsors. Significant Risk and Nonsignificant Risk Medical Device Studies (CDRH, January 2006)	Information Sheet Guidance for IRBs, Clinical Investigators, and Sponsors. Frequently Asked Questions About Medical Devices (CDHR, CBER, January 2006)

VII. REFERENCES TO OTHER APPLICABLE SOPS

SOP 412: Humanitarian Use Device

VIII. RESPONSIBILITIES

Title	Responsibility
Director, HSR	The Director, HSR (or designee) is responsible for reviewing incoming submissions and conducting preliminary review for either IND or IDE requirement.
Chair, CPHS	The Chair (or designee) is responsible for making sure IRB committee deliberations take into account whether an IND or IDE is required and confirming the validity of IND or IDE numbers, or delegating confirmation to designated committee member(s).
Designee	Responsible for making sure IRB committee deliberations take into account whether an IND or IDE is required and confirming the validity of IND or IDE numbers.

IX. ATTACHMENTS

Investigational New Drug and Device (IND-IDE) Support Office on the CHOP Research Institute Webpage (https://www.research.chop.edu/investigational-new-drug-and-device-support-program)

X. REVISIONS:

09-14-2006:	Initial approval date
06-10-2010:	Revised to update to new versions of FDA guidance documents and correction of formatting.
07-08-2010:	Revised to reflect AAHRPP's recommendations including methods for ascertaining that an IND or IDE is valid, Exemptions from IDE requirements, and expansion of the requirements for approval of studies using an NSR device.
03-07-2013:	Revise to clarify the investigator's and the IRB's responsibilities for determining whether or not an IND or IDE is required for approved drugs or devices.
09-25-2018:	Revised to include editorial changes and updated definitions.
06-09-2022:	Revised to include current processes, and requirements for radioactive and cold isotopes and updated definitions.

XI. APPROVAL:

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

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