1.0 Purpose:

1.1 This policy defines the applicability of the United States Code of Federal Regulations, 21 CFR Part 312 - Investigational New Drug Application (IND) and the procedures the Hartford HealthCare Human Research Protection Program (HHC HRPP) and IRB (Institutional Review Board) follow to determine whether an IND is needed for a clinical investigation.

1.2 An IND is a request to the FDA to allow the administration of investigational drugs to humans. It is also required if studies will be conducted on drugs or therapeutic biological products already licensed if the intent of the study is to generate new data that will lead to approval of new advertising claims, a new clinical indication, or a new formulation of the product. An IND or amendment to an existing IND is required to add a new study design, a new patient group, or a new clinical indication to the evaluation of a product that is under study but not yet marketed.

1.3 All non-exempt human subjects research and clinical investigations reviewed by the IRB are subject to this policy.

2.0 Definitions:

2.1 **Research** (45 CFR 46.102(l) - A systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.

2.2 **Human Subject** (45 CFR 46.102(e) - a living individual about whom an investigator (whether professional or student) conducting research (1) Obtains information or biospecimens through intervention or interaction with the individual, and uses, studies, or analyzes the information or biospecimens or (2) Obtains, uses, studies, analyzes, or generates Identifiable private information or identifiable biospecimens

- *Intervention* includes both physical procedures by which data or biospecimens are gathered (i.e., venipuncture) and manipulations of the subject or the subject's environment that are performed for research purposes.
- *Interaction* includes communication or interpersonal contact between investigator and subject.
- *Private information* includes information about behavior that occurs in a context in which an individual can reasonably expect that no observation or recording is taking place, and information which has been provided for specific purposes by an individual and which the individual can reasonably expect will not be made public (i.e., medical record). Private information must be individually identifiable (i.e., the identity of the subject is or may readily be ascertained by the investigator or associated with the information) in order for obtaining the information to constitute research involving human subjects.

2.3 **Sponsor -** 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. A person other than an individual that uses one or more of its own employees to conduct an investigation that it has initiated is a sponsor, not a sponsor-investigator, and the employees are investigators. [21 CFR 312.3(b)]

2.4 **Sponsor-investigator -** 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 requirements applicable to a sponsor-investigator under this part [21 CFR 312 Subpart D] include both those applicable to an investigator and a sponsor. [21 CFR 312.3(b)].

2.5 **Investigational new drug -** A new drug or biologic 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. [21 CFR 312.3(b)]

2.6 **Clinical investigation -** Any experiment in which a drug is administered or dispensed to, or used involving, one or more human subjects. An experiment is any use of a drug except for the use of a marketed drug in the course of medical practice. [21 CFR 312.3(b)]. The terms *research*, *clinical research*, *clinical study*, *study*, and *clinical investigation* are deemed to be synonymous [21 CFR 50.3(c) and 21 CFR 56.102(c)].

2.7 **Human subject -** An individual who is or becomes a participant in research, either as a recipient of the test article or as a control. A subject may be either a healthy human or a patient. [21 CFR 50.3(g) and 21 CFR 56.102(g)]

2.8 **Clinical Hold -** An order issued by the FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation. When on hold, subjects may not be given the investigational drug. When an on-going study is placed on clinical hold, no new subjects may be enrolled in the study, and patients already in the study should be taken off therapy unless specifically permitted by the FDA in the interest of patient safety [21 CFR 312.42 (a)]

3.0 Procedure:

3.1 Investigators submit all required protocol-related documents via the Research Application process to the IRB for review at a convened meeting.

3.2 When the research involves drug products or therapeutic biological products, the investigator is required to provide the IRB with sufficient information about the drug product, including FDA status, and its intended use to assess the risks and potential benefits to subjects.

3.3 The clinical investigation of a drug/biologic that is **not** approved for marketing requires submission of an IND application to FDA unless exempt according to 21 CFR 312.2. (See 3.4) An IND can be issued to a company, a government agency (i.e., NIH) or an individual investigator (sponsor-investigator). FDA notifies the sponsor in writing of the date it receives the IND application.

3.3.1 An IND goes into effect thirty (30) days after FDA receives the IND unless FDA notifies the sponsor that the investigations described in the IND are subject to a clinical hold under § 312.42; or

3.3.2 On earlier notification by the FDA that the clinical investigations may begin.

3.3.3 An investigator may not administer an investigational new drug to human subjects until the IND goes into effect and IRB approval has been granted.

3.4 The clinical investigation of a marketed product requires submission of an IND to the FDA unless **exempt** according to 21 CFR 312.2(b)(1) and the investigation does not involve an exception from informed consent requirements for emergency research (21 CFR 50.24). All of the following conditions must be met to be exempt:

3.4.1 The investigation is not intended to be reported to the 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 of labeling of the drug;

3.4.2 The investigation is not intended to support a significant change in the advertising for the product;

3.4.3 The investigation does not involve a route of administration or dosage level or use in a patient or other factor that significantly increases the risks (or decreases the acceptability of the risks) associated with the use of the drug product;

3.4.4 The investigation is conducted in compliance with the requirements for institutional review set forth in 21 CFR 56 and with the requirements for informed consent set forth in 21 CFR 50; and

3.4.5 The investigation is conducted in compliance with the requirements of 21 CFR 312.7 (promotion and sale of drugs).

3.4.6 Research is not intended to invoke 21 CFR 50.24 (exception from informed consent requirements for emergency research).

3.5 The exemption applies to marketed drug or therapeutic biological products being evaluated for safety and efficacy or effectiveness and marketed drug products used as comparators as well as products that will be administered to study human physiology or as part of a procedure or test required by the protocol (ancillary drugs).

Note: Use of a marketed product for an indication not in the approved labeling, when the intent is the “practice of medicine,” does not require an IND application. This is considered “Off-label use.”

3.6 When a lawfully marketed botanical dietary supplement is being studied for its effect on diseases (i.e., to cure, treat, mitigate, prevent or diagnose disease including its associated symptoms) it is considered an investigational new drug and is subject to the part 312 IND requirements.

3.7 When a radioactive drug is used in humans for research intended to obtain basic information regarding the metabolism (including kinetics, distribution, and localization) of a radioactively labeled drug or regarding human physiology, pathophysiology, or biochemistry, but **not** intended for immediate therapeutic, diagnostic, or similar purposes or to determine the safety and effectiveness of the drug in humans for such purposes (i.e., to carry out a clinical trial), the radioactive drug is not an investigational drug subject to the Part 312 IND requirements. However, the research is subject to review and approval by the Radiation Safety Officer (RSO).

3.7.1 If the research is designed to conduct a clinical trial of a radioactive drug, the radioactive drug is an investigational new drug and is subject to the Part 312 IND requirements and must be approved by the RSO.

3.8 When an individual investigator holds an IND, s/he assumes all of the responsibilities of the sponsor. The sponsor-investigator must be knowledgeable of the regulatory requirements in Part 312 IND requirements and be familiar with FDA guidance documents.

3.8.1 Sponsor-investigators are responsible for establishing recordkeeping and retention systems that comply with the requirements in Subpart D – *Responsibilities of Sponsors and Investigators.*

Note: The FDA may inspect sponsor-investigators' records at any time. Sponsor-investigators are held to the same recordkeeping requirements as corporate or government sponsors. The need to establish good recordkeeping systems before the clinical investigation begins will make FDA inspections easier and minimize the likelihood that an inspection will result in issuance of a Form FDA 483 citing observations of objectionable practices.

3.8.2 Investigators are responsible for maintaining control of the investigational drug, including receipt, storage and distribution, and should include a description of the procedure(s) that will be used when submitting materials to the IRB for review.

3.9 If the IRB determines that an IND is needed, the investigator must provide the IRB with 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.

3.9.1 To prevent situations where researchers begin studies that require regulatory authority approval, such as an IND, before the FDA has issued a number, the IRB will evaluate whether the IND number is valid. Validation will be done by determining that an approval number (IND) granted by the FDA matches the sponsor protocol, or communication from the sponsor, or communication from the FDA.

3.9.2 In the case of an investigator-held IND, the number should match information provided by the government regulatory agency.

3.9.3 IRB approval for any clinical investigation of an investigational drug product will not be given unless the IND is in effect as defined in § 312.40(b)(1)(2).

3.10 **Drug Products not Manufactured by a Licensed Pharmaceutical Company**

3.10.1 Drug products with INDs: when an individual or entity other than a licensed pharmaceutical company manufactures the drug product being investigated, the IRB will rely upon FDA review of the chemistry, manufacturing, and control information contained in the IND application.

3.10.2 Drug Products without INDs: when an individual or entity other than a licensed pharmaceutical company manufactures the drug being administered to human subjects and an IND is not required, the IRB will need a Certificate of Analysis.

3.11 Once the IRB determines whether an IND is required and the appropriate paperwork has been filed, it will continue the review.

3.12 Investigators and sponsors of approved protocols involving INDs must comply with all requirements as outlined in 21 CFR 312, subpart D. (See attached checklist)

3.13 In all cases, investigators must maintain control of investigational drugs so that they are used only in approved research protocols and under the direction of approved investigators. Such processes to ensure this control include:

3.13.1 The investigator, pharmacist, or other designated individual will maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or alternative disposition of unused products. These records will include dates, quantities, batch/serial numbers, expiration dates (if applicable), and the unique code numbers assigned to the investigational products and trial subjects.

3.13.2 Investigators should maintain records that document adequately that the subjects are provided the doses specified by the protocol and reconcile all investigational products received from the sponsor.

4.0 Documentation:

4.1 The HHC HRPP office will maintain all records related to the implementation of this policy, electronic communications and notifications to investigators, funding or regulatory agencies, etc.

4.2 Records will be archived for a period of at least six (6) years following the termination or completion of the research activities.

5.0 References:

5.1 21 CFR 50 – *Protection of Human Subjects*

5.2 21 CFR 56 – *Institutional Review Boards*

5.3 21 CFR Part 312 – *Investigational New Drug Application*

5.4 FDA Information Sheet Guidance: “Off Label” and Investigational Use of Marketed Drugs, Biologics and Medical Devices http://www.fda.gov/oc/ohrt/irbs/offlabel.html

5.5 Institutional Review Board Management and Function, Bankert, E. A., Amdur, R. J., 2nd Edition, 2006

6.0 Revision History:

Rev #	Initials	Effective Date	Description of Change(s)
01	EHP	7/1/11	Conversion to new policy template; significant expansion of policy
02	CLB	7/22/15	Addition of processes to control investigational drugs
03	CLB	3/15/20	General review. Expanded Section 3.9; updated definitions and regulatory citations.

Element I.7.A., I.7.B.