Status Active PolicyStat ID 17505857

Where the world comes for answers

Effective	3/1/2025
Next Review	2/29/2028
Owner	Susan Kornetsky: Manager
Department	Research
Applicability	Boston Children's Hospital- Policies & Procedures

Drugs, Biologics, and Dietary Supplements Policy/ Procedure

Internal Approval

SVP, Research Administation

EVP, Chief Scientific Officer

Scope

This policy applies to the Boston Children's Hospital (BCH) Research department and the respective staff.

Definitions

Investigational New Drug (IND) Application: a request for authorization from the Food and Drug Administration (FDA) to administer an investigational drug or biological product to humans

Investigational use: the use of an investigational product in the context of a clinical study protocol [21 CFR 312.3(b)]. When the principal intent of the investigational use of a test article is to develop information about the product's safety or efficacy, submission of an Investigational New Drug (IND) may be required.

Off-label use: When the FDA approves a drug or biologic it also includes the indications for which is it approved. Variance from the intended use is referred to as "off label use".

Sponsor-Investigator: An individual who both initiates, 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.

Policy Statements

This policy describes the various regulatory mechanisms for obtaining, testing, and using drug and biologic products in compliance with federal and state regulations pertaining to clinical investigations

Research at Boston Children's Hospital that involves the **investigational use** of drugs, biologics, and dietary supplements must conform to U.S. Food and Drug Administration (FDA) regulations, Department of Health and Human Services (HHS) regulations, and Massachusetts state regulations (94C MGL 8).

FDA regulations have additional requirements for clinical investigations that involve the off-label use of an approved product or biologic, if it is used in a manner for which it is not approved. FDA regulations for investigational new drug (IND) requirements are outlined in 21 CFR 312. Regulations on drug products can be found in 21 CFR 314 and regulations on biological products are in 21 CFR 600.

Massachusetts state regulations (94C MGL 8) require investigators who use an investigational new drug (IND), or the **investigational use** of any drug in schedules I – VI, in a research protocol to register for Massachusetts Controlled Subject Registration (MCSR) license.

Current federal law requires that a drug be the subject of an approved marketing application before it is transported or distributed across state lines. Because a sponsor will most likely ship the investigational drug to clinical investigators in other states, they must seek an exemption from that legal requirement.

1. The IND is the means through which the sponsor technically obtains an exemption from the FDA.
2. The IND regulations are detailed in 21 CFR 312.

Exemptions from IND Requirements

Federal regulations also allow for certain types of studies to be exempt from the IND regulations. Per 21 CFR 312.2, clinical investigations of a drug product that is lawfully marketed in the United States may be exempt from the requirements of the IND regulations, provided that all of the following conditions apply:

1. The study is not intended to be reported to the FDA as a well-controlled study in support of a new indication or use; or support any significant change in the drug's labeling;
2. The study is not intended to support a significant change in the advertising for a prescribed drug;
3. The study does not involve a change in route of administration, dosage level, patient population, or other factors that significantly increases the risks associated with use of the drug product;
4. The study complies with IRB evaluation and informed consent requirements; and
5. The study sponsor and/or investigator do not represent in a promotional context that the drug is safe and effective for the purposes in which it is under investigation.

When research involves the use of a drug other than the use of a marketed drug in the course of medical practice, the regulations also provide for additional exemptions from the IND regulations:

1. A clinical investigation involving an in vitro diagnostic biological product that meets all of the following criteria:
    a. Involves one or more of the following: blood grouping serum, reagent red blood cells, 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.
    c. The diagnostic test is shipped in compliance with 21 CFR 312.160 C.
2. A clinical investigation involving use of a placebo if the investigation does not otherwise require submission of an IND. (See 21 CFR 312.2 for a full description of exempt categories)

It is the responsibility of the Sponsor (including Sponsor-Investigator or Principal Investigator) to justify why a proposed study meets the requirements for exemption from the IND regulations.

1. Boston Children's Hospital's Regulatory and Education Program, in conjunction with the IRB, will determine whether the justification is sufficient to proceed, or whether confirmation by the FDA is necessary.
2. Investigators are advised to review the FDA Guidance document, *Investigational New Drug Applications (INDs) — Determining Whether Human Research Studies Can Be Conducted Without an IND*.

Conducting a Study in Accordance with IND Regulations: Investigator and Sponsor-Investigator Responsibilities

Investigator Responsibilities

Responsibilities of an investigator participating in a study under an IND are detailed in Subpart D of 21 CFR 312. For all investigations subject to IND regulations:

1. The investigator is required to be knowledgeable about the requirements of FDA regulations and
2. Must be listed on a *FDA Form 1572* in order to administer an investigational product.

At the time of continuing review, the IRB may request additional documentation to be confirm the investigator is following the IND requirements.

Sponsor-Investigators Responsibilities

Regulatory responsibilities for investigators and sponsors are detailed in 21 CFR 312 subpart D. A Sponsor-Investigator is responsible for all requirements as both a sponsor and an investigator.

Prior to IRB approval of a protocol, any BCH staff member holding an IND, either as the Sponsor or Sponsor-Investigator, must meet with Boston Children’s Hospital’s Regulatory and Education Program to:

1. Review the responsibilities of a Sponsor or Sponsor-Investigator.
2. Discuss study feasibility in context of available BCH resources and services.

Dispensing and Storage of Investigational Drugs and Drugs used in research protocols

All investigational drugs and drugs used for research protocols must be stored and dispensed from the pharmacy and used only under the direct supervision of the Principal Investigator (PI).

1. Investigational drugs must be shipped to the pharmacy and should not be stored in offices and clinic areas.
2. Industry sponsored studies may require inspection of the pharmacy's Investigational Drug Study Area before Boston Children's Hospital is used as a study site.
3. In all cases where study drugs are to be dispensed, the PI or a designee must contact the Pharmacy's Investigational Drug Study Service (ext. 2014 or 6803) to arrange for:
    a. shipping location
    b. storage
    c. dispensing instructions
    d. compounding
    e. blinding procedures
    f. record keeping
    g. other areas of pharmacy involvement.

Procedures

Investigational New Drug (IND) Application Process

It is the responsibility of the Sponsor-Investigator to submit an IND application to the FDA for studies which must be conducted under an IND. The IND application must adhere to the requirements outlined in 21 CFR 312.23.

Boston Children's Hospital Institutional Review Process

As part of the institutional review process, the Regulatory and Education program will meet with all Investigators seeking to submit an IND to the FDA to:

1. Review the proposed protocol
2. Review requirements of the institution and of sponsoring an IND
3. Provide recommendations for how the Investigator can meet their regulatory obligations.

FDA Submission

1. Once the IND is submitted, the sponsor must wait 30 calendar days before initiating any clinical trials.
2. During this time, the FDA reviews the IND for safety to assure that research subjects will not be subjected to unreasonable risk.
3. At the end of this 30-day review period, the FDA may issue a "Study May Proceed" letter or a clinical hold letter.

Information to be submitted with the IRB Application

Complete IND information must be submitted with any protocol submitted to the IRB that involves an investigational drug or biologic.

1. Investigators are required to submit IND information provided by the sponsor, or if the investigator is also the sponsor a copy of the letter from the FDA that assigns the IND.
2. IRB cannot approve the protocol until all IND information is complete.
3. Protocol administrators will be responsible for making sure this information is obtained prior to release of the IRB approval notification and informed consent document.
4. If there is any question as to whether an IND is required, the IRB may require, as part of the review and approval process, that the investigator contact the Boston Children's Hospital Regulatory and Education Program or the FDA to discuss the protocol and to determine if an IND is required.
5. Investigators who propose to use investigational or marketed drugs for unapproved indications must also follow FDA regulations 21 CFR 50 and 56.
    a. For the most part, the FDA regulations are the same as HHS regulations 45 CFR 46. The regulations are similar with regard to IRB organization, composition, procedure, record keeping, and criteria for approval of research protocol, and informed consent documentation.
    b. At the time of a continuing review, if an investigator is the sponsor of an IND, a copy of the annual report to the FDA will be requested.

Use of a marketed drug or biologic in a manner for which it is not approved: Off Label Use and Investigational Use

"**Off Label Use**"

Good medical practice and patient interest require that physicians use commercially available drugs and biologics in a knowledgeable way and with sound judgment. If a physician uses a product for an indication that is not in the approved labeling, it is their responsibility to be well informed about the product and to base its use on firm scientific rationale and sound medical evidence. Use of a product for an individual patient in this manner may be considered "off label use" and "medical practice." This does

not require submission of an IND or a protocol to the IRB. The IND regulations do not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.

"**Investigational Use**"

Approved drug and biologic products may also be utilized in clinical trials. When the principal intent of the investigational use of a test product is to develop information about the product's safety or efficacy, submission of a protocol to the IRB is required. This is usually performed as a protocol with a hypothesis for a group of defined patients. In this situation the intent is not solely to treat one patient but to look at a group of patients to answer a specific, predetermined set of questions.

FDA has stated that whether an IND is needed to conduct a clinical investigation of a marketed drug primarily depends on the intent of the investigation and the degree of risk associated with the use of the drug in the investigation.

1. A clinical investigation of a marketed drug is exempt from the IND requirements if all of the criteria for an exemption in 21 CFR 312.2(b) are met.
2. When there is a question as to whether the use of a marketed drug or biologic for an unapproved indication requires an IND, the investigator is advised to speak to Boston Children's Hospital's Regulatory and Education Program or to contact the FDA directly.
3. The IRB may require that an investigator contact the Boston Children's Hospital Regulatory and Education Program or FDA if this has not been done at the time of IRB review, and documentation of the determination is required.

Expanded Access of Investigational Drugs

The use of investigational drugs and biologics is usually limited to subjects enrolled in clinical trials under an IND. However, test articles may show some promise before the trials are completed. When there is no satisfactory standard treatment for a serious, a life-threatening, or a debilitating condition, the FDA has a mechanism that allows expanded access to the drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, subjects are generally willing to accept greater risks from test articles that may treat life-threatening and debilitating illnesses.

Dietary Supplements

The increased use of supplements has led to an increase in research. The FDA has finalized rules that define the types of statements that may be made concerning the effects of dietary supplements on the structure or function of the human body.

When a clinical investigation is intended to evaluate the dietary supplement's ability to diagnose, cure, mitigate, treat, or prevent a disease, an IND is usually required.

1. The investigator is advised to consult with the Boston Children's Hospital's Regulatory and Education Program or with the FDA when developing a protocol that involves the use of dietary supplements.
2. The IRB may also require that the FDA be contacted, if the investigator has not already done

so.

Massachusetts Controlled Substance Registration (MCSR)

Massachusetts Regulations (94C) for Registration of Investigational Drugs and Schedule II Drugs in Research Massachusetts law requires the registration of investigators who use investigational and Schedule II drugs in research protocols.

Under Massachusetts' Controlled Substance Act (Chapter 94C), research projects and studies involving an investigational new drug (IND) as defined in 21 CFR 312.3, or the **investigational use** of any drug in schedules I-VI are required to register for Massachusetts Controlled Substance Registration (MCSR) license (Section 8: Research Projects and Studies).

1. For studies involving the **investigational use** of any drug in schedules I-V, the investigator must apply for their own individual Researcher MCSR and with US Drug Enforcement Administration (DEA) for the same schedule.
2. For studies involving an IND or the **investigational use** of a schedule VI drug, only the Researcher MCSR is required (not DEA). In such case, the investigator may obtain an individual Research MCSR, or the Department Chair may opt to assume responsibility for all research investigators with drug studies within their departments under one application.
3. For any new study that is not covered by an MCSR license (either by investigator or Department Chair), it is the Investigator's responsibility to notify their Department Chair and decide who should hold the license. If the Department Chair already has an active MCSR license, the protocol can be added through an application amendment (no fee).
4. Each applicant (whether individual investigator or Department Chair) is responsible for the following:
    a. determining drug schedule and if applicable, obtain DEA license
    b. ensure MCSR license exist for each location drug will be stored.
    c. ensuring licenses are amended as required
    d. renew MCSR license annually
5. If the Department Chair submits on behalf of the investigators in their department, the Researcher MCSR license will be in their name. The Department Chair must include a list of all protocols covered under this license and each protocol should specify the following:
    - PI Name
    - Protocol Title
    - Name of Study Drug(s)/Biologic
    - Storage Location for each study drug/biologic
    - Drug Schedule (I-VI), if applicable
    - IND Status: IND Number
    - IRB Approval Date

- FDA Form 1572
- Please note: a department chair can only include protocols involving an IND or investigational use of schedule VI. If a study drug/biologic is Schedule I-V, the Department Chair cannot include this protocol. The PI is responsible to obtain and remains responsible for their own individual Researcher MCSR license and DEA license for the same schedule for the duration of the protocol.

6. If the Department Chair submits on behalf of the investigators in their department, the Researcher MCSR license will be in their name. The Department Chair must include a list of all protocols covered under this license.
7. The Regulatory and Education Program maintains a database of all current MCSR licenses and will automatically send out reminder notifications starting 90 days prior to expiration. Department Chairs' notification will include an updated list of all active studies. At this time, if is discovered that an active protocol does not have an MCSR, the Regulatory and Education Program will notify both the PI and Department Chair to ensure compliance.

Related Content

- U.S. Food & Drug Administration CFR – Code of Federal Regulations
  - 21 CFR.312: Investigational New Drug Application
  - 21 CFR 312.2: Investigational New Drug Exempt Categories
  - 21CFR.314: Applications for FDA Approval to Market a New Drug
  - 21CFR.600: Biological Products
- U.S. Food & Drug Administration Guidance
  - ***Information Sheet Guidance for Sponsors, Clinical Investigators, and IRBs: Frequently Asked Questions – Statement of Investigator (Form FDA 1572)***
  - ***Investigator-Initiated Investigational New Drug Applications***:
  - ***Investigational New Drug Applications (INDs) – Determining Whether Research Studies Can be Conducted Without an IND***
- Massachusetts General Law
  - Chapter 94C Section 8: Research projects and studies
  - Department of Public Health 105 CMR 700.009: Research Involving Controlled Substances
- IRB Policy
  - Expanded Access – Investigational Drugs (For additional information on expanded access for investigational drugs)
- Boston Children's Hospital Resources
  - CRO Regulatory & Education Program: Regulatory Support

Approval Signatures

Step Description	Approver	Date
Co-chair Approval	David Davis	3/1/2025
Site Administrator: Education/ Training Requirement	Dwight Mayfield	2/25/2025
Steering Committee	Dwight Mayfield	2/25/2025
Required Departmental Review/Approval	August Cervini	2/2/2025
Committee Chair(s)	Susan Kornetsky: Manager	2/1/2025
Contributor(s)	Susan Kornetsky: Manager	2/1/2025
Document Owner	Susan Kornetsky: Manager	2/1/2025

Applicability

Boston Children's Hospital- Policies & Procedures