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Owner	Susan Kornetsky: Manager
Department	Research
Applicability	Boston Children's Hospital- Policies & Procedures

Expanded Access – Investigational Drugs Policy/Procedure

Internal Approval

SVP, Research Administration

Scope

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

Policy Statements

This policy describes the various regulatory pathways for obtaining and using investigational drug (IND) and biologic products for the treatment of patients under expanded access mechanisms in compliance with federal regulations. The scope of this policy includes:

1. Single Patient INDs (emergency and non-emergency requests)
2. Intermediate-Size Patient Population Access
3. Treatment Wide IND/Industry-Sponsored Expanded Access Program

FDA Expanded Access of Investigational Drugs

The use of investigational drugs and biologics (i.e., "test articles") is usually limited to those enrolled in clinical trials under an Investigational New Drug (IND). However, certain test articles may show some therapeutic promise before the research trials are completed. For individuals with serious, life-threatening, or a debilitating condition for which there is no satisfactory standard treatment, the FDA has a mechanism that allows expanded access to the drugs before the clinical trials are complete. When no satisfactory alternative treatment exists, patients and their families may be willing to accept greater risks for the potential to mitigate symptoms or treat life-threatening and debilitating illnesses.

Expanded Access Approval Criteria:

- Patient has a serious disease or condition, or whose life is immediately threatened by their disease or condition
- No comparable *or* satisfactory alternative therapy to diagnose, monitor, or treat the disease or condition
- Patient enrollment in a clinical trial is not possible
- Potential patient benefit justifies the potential risks of treatment
- Providing the investigational medical product will not interfere with investigational trials that could support a medical product's development or marketing approval for the treatment indication

The FDA has the following regulatory pathways for access to investigational drugs or biologics:

- 21 CFR 312 Subpart I: Expanded access use of an Investigational New Drug (IND)
- 21 CFR 314: Drug products
- 21 CFR 600: Biological products

The FDA regulations require that Treating Physicians obtain both FDA and (whenever possible) IRB approval prior to treatment.

Emergency Use INDs

In emergent situations whereby a patient must be treated with a test article before it is feasible to formally submit an IND application, the FDA has a dedicated emergency expanded access office available to grant an Emergency Use Single Patient IND to Treating Physicians. The FDA has a mechanism to review and approve emergency requests rapidly (withing 24 hours). Once the FDA issues approval, the Treating Physician may treat the patient if there is no time to submit to the IRB prospectively. The IRB strongly recommends that Treating Physicians notify the IRB as soon as they apply to the FDA for a sIND so that we can provide IRB submission guidance.

NOTE: In cases whereby the **patient must be treated sooner than the 30-day FDA review period, the IRB strongly recommends the Treating Physician utilize the Emergency Use pathway** for sIND applications.

Refer to the FDA's website on Expanded Access for the comprehensive process.

Treating Physician responsibilities include (but are not limited to):

1. Once an Emergency Use sIND is granted, the physician-sponsor has 15 calendar days to submit the written application to the FDA.
2. The Emergency Use IND must be reported to the Boston Children's Hospital IRB within 5 working days.
    a. Any subsequent use of the test article is subject to IRB review prior to initiation of treatment.

When research is regulated by the FDA, the emergency use of a test article, other than a medical device, is a clinical investigation, the patient is a participant, and the FDA may require data from an emergency

use to be reported in a marketing application.

However, HHS regulations do not permit data obtained from patients to be classified as research involving human participants, nor permit the outcome of such care to be included in any report of a research activity subject to HHS regulations.

Informed Consent

The IRB strongly recommends the Treating Physician obtain informed consent prior to administration of the test article whenever possible. The IRB understands there may be emergent situations whereby obtaining informed consent prior to drug administration is not feasible due to the patient's medical condition.

The FDA requires informed consent to be obtained from the subject or the subject's legally authorized representative, unless both the physician-investigator and a physician who is not otherwise participating in the clinical investigation certify in writing all of the following (21 CFR 50.23(a)):

1. The subject is confronted by a life-threatening situation necessitating the use of the test article.
2. Informed consent cannot be obtained because of an inability to communicate with, or obtain legally effective consent from, the subject.
3. Time is not sufficient to obtain consent from the subject's legal representative.
4. No alternative method of approved or generally recognized therapy is available that provides an equal or greater likelihood of saving the subject's life.

Intermediate-Size Patient Population Access

In cases where more than a single patient will be treated with an investigational product (but fewer than a treatment IND/protocol), the FDA has a regulatory pathway for an intermediate-size patient population to access the investigational drug or biologic. The manufacturer or Treating Physician must be granted FDA approval of the IND before submitting to the local IRB. Intermediate Size expanded access protocol should be submitted to the IRB via CHeRP as a New Research Activity.

- An intermediate-size patient population IND is traditionally submitted by a single physician to treat multiple patients.
- The investigational product may or may not be under development for marketing.

Treatment IND/Protocol

A treatment IND (21 CFR 312.34 and 312.35) is a mechanism for a larger group of patients to access an investigational drug or biologic for the treatment of serious and life-threatening illnesses for which there are no satisfactory alternative treatments.

A treatment IND may be granted to the Sponsor after sufficient data demonstrate that the drug "may be effective" and does not have unreasonable risks. Data related to safety and side effects will be collected under treatment INDs which also serve to expand the body of knowledge about the drug.

There are four requirements that must be met before a treatment IND can be issued:

1. The drug is intended to treat a serious or immediately life-threatening disease.
2. There is no satisfactory alternative treatment available.
3. The drug is already under investigation, or trials have been completed.
4. The trial sponsor is actively pursuing marketing approval.

Treatment INDs and treatment protocols must be submitted to the IRB in CHeRP as New Research Activity.

Sponsor-Investigators Holding Patient Expanded Access INDs Responsibilities

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

Dispensing and Storage of Investigational Drugs and Drugs Used in Expanded Access Mechanisms

All investigational drugs and drugs used for expanded access must be stored and dispensed from the pharmacy and used only under the direct supervision of the Treating Physician who is listed in CHeRP as the Principal Investigator (PI).

1. Investigational drugs must be shipped to the pharmacy and should not be stored in offices and clinic areas.
2. 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 plan for:
    a. shipping location
    b. storage
    c. dispensing instructions
    d. compounding, blinding procedures
    e. record keeping
    f. other areas of pharmacy involvement.

Procedures

Single Patient Expanded Access Investigational New Drug (sIND) Application Process

Single Patient INDs are usually submitted by the Treating Physician and therefore, that physician becomes the Single Patient IND holder.

The Individual Patient Expanded Access IND application must contain:

a. ***FDA Form 3926*:** This form includes questions where the physician must describe the clinical history of the patient and proposed treatment plan. It is possible to attach a separate document if more information is needed.

b. **Physician qualification statement:** This information is usually provided in the format of the physician's curriculum vitae and medical license.

c. **Letter of Authorization**: An IND traditionally requires information about the toxicology studies and manufacturing information about the investigational product.

    a. A Letter of Authorization signed by the manufacturer enables the FDA to cross-reference the Drug Master File, rather than having the physician resubmit information.

    b. Usually, a Drug Master File by the manufacturer of the investigational product has been submitted to the FDA

IRB Application: Individual Patient Expanded Access

Treating Physicians must use the Individual Patient Expanded Access IRB submission to obtain IRB approval prior to treatment. This Smartform will ask for:

a. A description of the clinical history

b. Treatment plan of the patient

c. Documentation of FDA Approval (email is acceptable for emergency use)

d. Written consent form on the BCH Expanded Access Consent Form

When there is not sufficient time to obtain IRB approval, is also possible for treatment with an investigational product to begin prior to authorization from the IRB. If this occurs, the use of the investigational product must be reported to the IRB within 5 working days of the treatment initiation. This can also be reported in CHeRP with the Individual Patient Expanded Access form.

Related Content

- U.S. Food & Drug Administration
    - 21 CFR.312: Investigational New Drug Applications
    - ***FDA Form 3926***
- Massachusetts General Law
    - Chapter 94C Section 8: Research projects and studies
- IRB Policy
    - Drugs, Biologics, and Dietary Supplements
    - Requirements for Investigators Who are Also Considered Sponsors of New Drugs
- Boston Children's Hospital Resources
    - CRO Regulatory & Education Program: Regulatory Support

Approval Signatures

Step Description	Approver	Date
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Applicability

Boston Children's Hospital- Policies & Procedures