**Guide to Conducting Clinical Trials at Boston Children’s Hospital: Investigator-initiated IND Applications**

## Note: The content of this guide is based on the experience of the authors to date, based on the current regulations (as of December 2016). The FDA is the final authority in the filing of an Investigational New Drug Application.

### Some of the content in this document is taken directly from the FDA website at [http://www.fda.gov](http://www.fda.gov/). Use the hyperlinks embedded to go directly to the FDA’s website to obtain the most current information.

### The focus of this guide is the submission and maintenance of an Investigator-initiated Investigational New Drug (IND) Application and relevant resources for the conduct of studies under an Investigator-initiated IND. This type of IND is prevalent in academic settings where research trials are often developed to enhance scientific knowledge, study rare diseases, identify novel uses for already approved agents, or in studying dietary supplements, or nutriceuticals, used with the intention of preventing, curing, mitigating, or treating a human disease. Thus the intent of an Investigator-initiated IND is often different compared to their industry counterparts, in which the drug [development process](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm) is often thought of in a setting where agents are developed for widespread commercial use.

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# What is an IND?

An IND is a request to the FDA for authorization to administer an investigational drug or biologic to humans. Technically, an IND allows drugs and biologics that are not FDA approved to be shipped across state lines. Generally, INDs fall into two main categories: INDs for clinical trials and INDs for expanded access.

Types of [INDs](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/default.htm) for expanded access include:

* [**Emergency Use IND**](http://www.fda.gov/drugs/developmentapprovalprocess/howdrugsaredevelopedandapproved/approvalapplications/investigationalnewdrugindapplication/ucm090039.htm) allows the FDA to authorize use of an experimental drug in an emergency situation that does not allow time for submission of an IND in accordance with 21CFR, [Sec. 312.23](http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=21&amp;PART=312&amp;SECTION=23&amp;YEAR=1999&amp;TYPE=TEXT) or [Sec. 312.34.](http://frwebgate.access.gpo.gov/cgi-bin/get-cfr.cgi?TITLE=21&amp;PART=312&amp;SECTION=34&amp;YEAR=1999&amp;TYPE=TEXT) It is also used for patients who do not meet the criteria of an existing study protocol, or if an approved study protocol does not exist.
* **Single Use IND:** This IND is to obtain an unapproved drug for an individual patient. The physician should first verify the drug manufacturer will provide the drug. The link for instructions on filing a single use IND is located [here](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm107434.htm).
* **Expanded Access Submission- IND Application for Intermediate-Size Population:** These INDs are usually intended for patients who do not meet eligibility criteria for the clinical trials studying the drug, or for patients who have no other means to access the investigational drug (i.e. no longer being developed for commercial purposes or has been removed from the market).
* **Expanded Access Submission-Treatment IND Application:** These INDs are generally used to provide access to an investigational drug to a large number of patients while a marketing application for the drug is under review by the FDA.

An **Investigator-initiated IND** is submitted by an individual who both initiates and conducts an investigation, and under whose immediate direction the investigational drug is administered or dispensed. A physician investigator might submit an IND to propose studying an unapproved drug, or an approved product for a new indication or in a new patient population.

Please note that this guide will focus primarily on Investigator-Initiated INDs for clinical trials. Separate guides for the submission and maintenance of single use and emergency INDs have been created for Boston Children’s Hospital investigators.

The FDA’s primary objective in reviewing IND applications, regardless of study phase, is to ensure the safety and rights of subjects. ([312.22](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.22)) Keep in mind that the FDA does not “approve” IND applications (unlike the IRB, for example). An IND is “in effect” 30 days after the submission, unless the Sponsor is notified of a clinical hold or the Sponsor is notified that the study is exempt from IND regulations. (Described later in this document)

# The Roles of the Sponsor and the Investigator

The Code of Federal Regulations outlines different responsibilities for the Sponsor and the Investigator. For most Investigator-initiated IND applications, the PI takes on both roles and is the Sponsor-Investigator.

***Sponsor*** is defined as an entity that 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. (Recall that only an individual may be a Sponsor-Investigator.) Please note that BCH does not become a Sponsor, nor holds an IND. A Sponsor can also be known as an IND holder, meaning the IND is that company or individual’s name.

***Investigator*** means an individual who actually conducts a clinical investigation (i.e. under whose immediate direction the drug is administered or dispensed to a subject). In the event an investigation is conducted by a team of individuals, the investigator is the responsible leader of the team, generally known as the Principal Investigator (PI).

***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 requirements applicable to a Sponsor-Investigator under this part include both those applicable to an investigator and to a Sponsor. The responsibilities of a Sponsor-Investigator (also known as an IND holder) are discussed in more detail in section XIV.

# How to Start the IND Process

* 1. **Determining the need for an IND**

Determining if an IND is needed when the study is using a commercially available product is specified in the Code of Federal Regulations (CFR 312.2):

1. *Exemptions.* (1) The clinical investigation of a drug product that is lawfully marketed in the United States is exempt from the requirements of this part if **all** the following apply:
	1. 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;

(ii) 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;

(iii) 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;

1. 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; and
2. The investigation is conducted in compliance with the requirements of [312.7](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.7). (Promotion and charging for investigational drugs.)

### Item (iii) is often the subject of debate in academic settings, especially in pediatric settings that involve children with life threatening illness, chronic illness, genetic syndromes, neonates, and in situations where limited pediatric experience is available. It is well known that many FDA approved drugs are not labeled for pediatric use. The submission to the FDA need not be a complete application, but should include at a minimum a form 1571, form 1572, a protocol, and reference to the drug to be used (i.e. package insert). The FDA will either indicate an IND is required by requesting materials to complete the application or will determine that the application is exempt.

### It is not always required at Boston Children’s Hospital to first obtain a formal determination from the FDA that the application is exempt. An investigator may provide a justification for an IND exemption in the submission to the IRB, which will be reviewed by the BCH Regulatory Affairs Specialist (during the drug-device ancillary review process). The FDA allows investigators to make this determination without involvement from the FDA, as long as the IRB agrees with this justification. In the event that the Regulatory Affairs Specialist and BCH IRB cannot make a determination, the IRB will ask the investigator to submit to the FDA to request an IND exemption.

Even if it is determined that an IND is not required for a particular study, all applicable rules pertinent to human subject research apply.

# What Does an [IND Application](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm343349.htm) contain?

[Information for Sponsor-Investigators Submitting IND’s](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071098.htm)

The IND application must contain information in three broad areas:

1. **Animal Pharmacology and Toxicology Studies** - Preclinical data to permit an assessment as to whether the product is reasonably safe for initial testing in humans. Also included is any previous experience with the drug in humans.

### **Manufacturing Information** - Information pertaining to the composition, manufacturer, stability, and controls used for manufacturing the drug substance and the drug product. This information is assessed to ensure that the company can adequately produce and supply consistent batches of the drug.

A training course on the Chemistry, Manufacturing and Control (CMC) Section of the IND can be found at this [link.](http://www.accessdata.fda.gov/cder/cmc/menu.htm)

1. **Clinical Protocols and Investigator Information** - This section contains detailed protocol(s) for the proposed clinical study(s) to assess whether the initial-phase trials will expose subjects to unnecessary risks. Information is also required to document the qualifications of clinical investigators – professionals (generally physicians) who oversee the administration of the experimental compound – to assess whether they are qualified to fulfill their clinical trial duties. In addition, commitments are made to obtain informed consent from the research subjects, to obtain review of the study by an IRB, and to adhere to the investigational new drug regulations.

A protocol may be submitted by Investigators with M.D. degrees, Ph.D. degrees, or neither; however, the protocol must provide for appropriate clinical care and oversight of the subjects.

# How is an IND Submission Arranged?

The template for an IND submission can be found in Appendix A.

# What are Letters of Cross Reference?

In academics, investigators often explore novel uses of drugs that are already FDA approved for other uses. For drugs that are already approved and marketed, it is acceptable to indicate in the application that the drug is FDA approved/commercially available and provide the New Drug Application (NDA) number and package insert. Investigators may want to approach the company who manufactures the approved drug to provide a letter of cross reference and possible financial support. If the project supports the business strategy of the company, they may be willing to provide such support.

If the investigational agent is not FDA approved and is still under an Investigational New Drug status by the manufacturer, then a letter of cross reference by the manufacturer is required. By providing a letter of cross reference, the company which manufactures the agent gives the FDA permission to cross reference all of the existing files on the product. This letter of cross reference potentially eliminates the need to provide extensive detail regarding chemistry and manufacturing, provided that the agent will not be altered in any way for administration. If alteration of the product will occur, then details of such must be provided. For example, if the drug will be further diluted or repacked into different dose levels.

A confidentiality agreement (Confidential Disclosure Agreement or CDA) and Material Transfer Agreement (MTA) is typically required in order for the company to provide the drug and to give the Investigator access to the Investigator’s Brochure (IB). All agreements must be reviewed by the Clinical Trials Business Office (ctbo@childrens.harvard.edu) before an investigator can sign.

In order to request a letter of cross reference, two resources to locate who holds the NDA include the FDA Website [Drugs@FDA](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm) or the “Electronic Orange Book,” available on line at <http://www.fda.gov/cder/ob/>.

If the manufacturer of a commercially available product (FDA approved) does not want to provide a letter of cross reference, the IND can still be submitted. In place of the letter, state that the drug is commercially available, and provide a product insert for the specific product being used. This insert can be provided by the pharmacy, the Physician’s Desk Reference, or the FDA Website [Drugs@FDA](http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm).

# How do I submit the IND?

The documents should be submitted in binders (a red binder for original documents and one blue and one grey for the two copies) and tabbed. Several FDA staff members will review the IND concurrently. Ease of review is imperative so that reviewers can easily find each document behind the appropriate tab. Including a table of contents is very beneficial.

The initial IND submission (and any other submission) should be accompanied by a Form 1571 and numbered sequentially, with the initial filing labeled as “0000.” An original and two photocopies are required. IND Forms and Instructions can be found at this [link](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/ucm071073.htm).

FDA Form 1571 can be thought of as the Sponsor’s cover letter to the FDA, and is included in any correspondence to the FDA pertinent to the IND, sent *by a Sponsor* to the FDA. Indicate on the form what type of correspondence that is being sent (e.g., protocol amendment, addition of new investigator, safety report, etc.)

### Form 1572 is a document that an *investigator* signs and submits to the *Sponsor*. Those individuals listed on the 1572 should be those who have the capacity to make direct or significant impact on data, including protocol-related decisions. The 1572 may need to be updated throughout the study, such as with personnel changes at a site, change in lab facilities, IRBs, etc. The key point is that it is the *Sponsor’s* duty to maintain current CVs, training records, and delegation logs outlining who is qualified and authorized to perform specific protocol related functions.

### After compiling the entire IND submission, send the original and two photocopies to the following address:

**For a Drug:**

Food and Drug Administration
Center for Drug Evaluation and Research
Central Document Room
5901-B Ammendale Rd.
Beltsville, Md. 20705-1266

**For a Therapeutic Biological Product:**

Food and Drug Administration
Center for Drug Evaluation and Research
Therapeutic Biological Products Document Room
5901-B Ammendale Road
Beltsville, MD 20705-1266

### Please note that if you have prior correspondence with an FDA reviewer regarding this IND application, you may be directed to send future correspondence, including the IND application, directly to the appropriate review division.

# What kind of feedback do I receive, and when?

In about two weeks’ time, the Sponsor will receive a letter by regular mail delivery with the log in date (date of receipt) and assigned IND number. Include this IND number on all future correspondence with the FDA. Also included will be the address where future submissions should be sent for this IND, as well as the name and phone number of the project manager at the FDA for questions regarding the submission. Please note that this acknowledgement of receipt should not be interpreted as review or approval of your IND application.

**Remember that studies cannot be initiated until 30 days after the *date of receipt* of the IND by the FDA unless the Sponsor receives an earlier notification by the FDA that the study(s) may begin. The Sponsor will also be notified via phone (most likely), fax, or mail if the application has been placed on clinical hold.**

Within the 30 day window in which the FDA is reviewing the application, if the FDA has a question, they may call the Sponsor; if the question is resolved satisfactorily within the 30 day window, there is no clinical hold.

If the FDA has additional, more substantial, concerns, the FDA will provide a detailed letter (known as a clinical hold) of what is needed to complete the review and eventually release the application from clinical hold. Remember that there are many individuals reviewing the application, each with their own specific purpose. The clinical reviewer may request additional lab tests or lab time points because of a safety concern regarding the investigational agent. If the application includes CMC (Chemistry, Manufacturing, and Control) data, the CMC/product reviewer may request additional information. The FDA may also ask for potentially lengthy and costly pre-clinical research, and it will be up to the Sponsor as to whether or not to pursue the requested research or withdraw the application.

In responding to the clinical hold, the response letter should be a point by point response to each issue with supporting documentation included. The letter should indicate “Clinical Hold Complete Response.” A 1571 should accompany this response, with an updated serial number.

### In addition to the clinical hold issues, the FDA clinical hold letter may also include issues that are of importance but are not the reason for the clinical hold. These issues do not require immediate response and should not be responded to with the clinical hold response, but should be thoroughly examined and a response provided to the FDA in a subsequent correspondence.

See also: [Guidance Document for Clinical Hold Response](http://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm080581.pdf)

If a clinical hold is placed on an IND that has been open and enrolling subjects, this may be due to a number of reasons, including abnormal findings in long term animal studies or concern over excessive adverse events. Regardless, this is a very serious situation which may require extensive additional monitoring or follow up of study subjects.

**A. When is a Pre-IND Meeting Needed?** (Excerpt from [Guidance Document](http://www.fda.gov/Drugs/DevelopmentApprovalProcess/SmallBusinessAssistance/ucm069906.htm))

Sometimes, Sponsors wish to discuss their IND application with the FDA prior to submission. This is not a requirement for each IND submission, but used primarily when there may be safety or development concerns about the drug/biologic. There are three types of meetings: [Type A, B, and C](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM153222.pdf). Type A meetings are defined as meetings that are needed for an otherwise stalled drug development program to proceed. Type C meetings are those that are other than a Type A or B.

Type B meetings are, for our purposes, the most commonly requested. Type B meetings are

1. pre-IND meetings ([21 CFR 312.82](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.82)) (our focus);
2. certain end of Phase 1 meetings (21 CFR 312.82);
3. end of Phase 2/pre-Phase 3 meetings ([21 CFR 312.47](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.47)); and
4. pre-NDA/BLA meetings (21 CFR 312.47).

For applications involving a commercially marketed product, Pre-IND meetings are generally not necessary. Pre-IND meetings are especially helpful if the drug/biologic/vaccine in question is generated in an academic medical center for which great details are needed in the IND application regarding toxicology, animal studies, manufacturing, etc. They can also be useful when a new route of administration or other alteration of a previously-approved product is proposed.

### These are most often teleconferences, not face-to-face meetings, and are usually allotted 60-90 minutes, so preparation is important for the success of these meetings. These are non-binding meetings; they are provided as general guidance. Official meeting minutes are provided by the FDA. Even if the investigator has fulfilled all of the recommendations from a Pre-IND meeting, it is still possible that the IND application will be placed on clinical hold.

**B. How to Request a Type B Meeting**

A Sponsor who is interested in meeting with the Agency should submit a written request (i.e., letter or fax) to the appropriate FDA office. For Drugs, the Center for Drug Evaluation and Research (CDER), is the office to contact. Note that CDER is broken down into many different divisions, so it may take a little leg work to locate the correct division. See also: [CDER Pre-IND Consultation Contacts](http://www.fda.gov/downloads/Drugs/DevelopmentApprovalProcess/HowDrugsareDevelopedandApproved/ApprovalApplications/InvestigationalNewDrugINDApplication/Overview/UCM166356.pdf)

Prior to submitting a written request for a meeting by fax or email, the Sponsor should contact the appropriate review division to determine to whom the fax or email should be directed and to arrange for confirmation of receipt of the fax. All faxed or emailed meeting requests should subsequently be submitted in hard copy (in triplicate) to the Central Document Room. Please note that the clock does not start until the FDA receives the hard copies.

To make the most efficient use of FDA resources, any meeting request should include adequate information for the appropriate FDA component to determine the utility of the meeting and to identify the staff necessary to discuss proposed agenda items.

The template for a meeting request is included in Appendix B.

The Division Director or delegate in the FDA who receives a request for a meeting will determine whether to hold the meeting. The review division should respond to the Sponsor or applicant *within 14 days* of receipt of the meeting request. If the FDA agrees to the meeting, a letter or fax will be provided that includes the date, time, length, and place (if applicable) of the meeting as well as the expected FDA participants.

### The FDA honors requests for Type B meetings in most circumstances. The actual date of the meeting is set by the FDA and should be scheduled to occur within 60 days of the receipt of the request.

**C. What is the Content of Type B Meeting Information Packages?**

The Sponsor should submit an information package to the appropriate Division Director in the Center for Drug Evaluation and Review (CDER) or the Center for Biologic Evaluation and Review (CBER) with product review responsibility. The information package should provide summary information relevant to the product(s) and any supplementary information. This information package should be received by the FDA approximately 4 weeks prior to the meeting. The FDA will indicate the specific deadline for this information package in their meeting request receipt acknowledgement.

The FDA may postpone or cancel a meeting if supporting documentation essential for a productive meeting has not been received by the Agency within the prescribed time frames. *Failure to submit an adequate information package within the time frames will be considered a request by the Sponsor or applicant to cancel the meeting.*

The FDA will explain the basis for finding that the information package is deficient. To schedule another meeting with the Agency, the S

ponsor will need to submit another meeting request to the appropriate Division Director.

### To facilitate the FDA's review be sure to provide information on the product, key pre-clinical data, and the proposed clinical study. Questions should be grouped by type: product, preclinical, clinical and regulatory.

Organize the contents of the information package according to the proposed agenda. A *fully paginated* document with a table of contents, appropriate indices, appendices, cross references, and tabs differentiating sections is recommended. The project manager or division contact can advise on the numbers of copies needed. The cover letter accompanying the information package should clearly identify the date, time, and subject of the meeting. Although the contents of the information package will vary depending on the product, indication, phase of drug development, and issues to be discussed, the template for information packages is found in Appendix C.

### CDER and CBER handle their Pre-INDs each in a slightly different manner. For CBER, the members of the FDA review team will review the package and will review and respond with draft responses prior to the meeting. These responses are sent to the Sponsor who can then cancel the meeting if the answers provided are satisfactory or pursue the meeting focusing on selected issues or to review the responses. CDER may provide responses before the meeting, but this does not always happen.

### A meeting summary (minutes) will be provided by the FDA approximately 30 days after the meeting.

# Annual Reports

Annual Reports to the FDA are due within 60 days of the anniversary date of the IND. Please note that this due date may be different than your IRB approval and subsequent continuing review due date. Annual reports are required each year that the IND is in effect, regardless of whether the study began or subjects were enrolled.

Annual Reports: [312.33](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.33)

A template for an IND annual report is included in appendix D.

# Amendments to an Existing IND

Once an IND is in effect, a Sponsor-Investigator may wish to make changes. There are several different types of IND amendments.

**Protocol Amendment: New Protocol**

A Sponsor can have multiple protocols under a single IND. For example, if the Sponsor is studying drug XYZ under IND #11,111 for condition A, and then decides to also want to study under a separate protocol condition B, then this paragraph applies:

1. ***New protocol****.* Whenever a Sponsor intends to conduct a study that is not covered by a protocol already contained in the IND, the Sponsor shall submit to FDA a protocol amendment containing the protocol for the study. Such study may begin provided two conditions are met: (1) The Sponsor has submitted the protocol to FDA for its review; and (2) the protocol has been approved by the Institutional Review Board (IRB) with responsibility for review and approval of the study in accordance with the requirements of part 56. The Sponsor may comply with these two conditions in either order.

### The 30 day waiting period involved with an initial IND filing normally does not apply to new protocols being added to an existing IND; however, the FDA can still ask questions or issue a clinical hold. Although this means that the study can be initiated, some Sponsor-iIvestigators find it good practice to wait 30 days to ensure that a clinical hold will not occur.

As the new protocol is being developed, you will need to update the company that has provided the letter of cross reference. The company will want to review the protocol and may need to provide an additional or updated letter of cross reference.

**Protocol Amendment: Change in Protocol**

If there is an existing protocol being amended, this section applies:

1. ***Changes in a protocol****.* (1) A Sponsor shall submit a protocol amendment describing any change in a Phase 1 protocol that significantly affects the safety of subjects or any change in a Phase 2 or 3 protocol that significantly affects the safety of subjects, the scope of the investigation, or the scientific quality of the study. Examples of changes requiring an amendment under this paragraph include:
	1. Any increase in drug dosage or duration of exposure of individual subjects to the drug beyond that in the current protocol, or any significant increase in the number of subjects under study.
	2. Any significant change in the design of a protocol (such as the addition or dropping of a control group).
	3. The addition of a new test or procedure that is intended to improve monitoring for, or reduce the risk of, a side effect or adverse event; or the dropping of a test intended to monitor safety.

(2)(i) A protocol change under paragraph (b)(1) of this section may be made provided two conditions are met:

1. The Sponsor has submitted the change to FDA for its review; and
2. The change has been approved by the IRB with responsibility for review and approval of the study. The Sponsor may comply with these two conditions in either order.
3. Notwithstanding paragraph (b)(2)(i) of this section, a protocol change intended to eliminate an apparent immediate hazard to subjects may be implemented immediately provided FDA is subsequently notified by protocol amendment and the reviewing IRB is notified in accordance with 56.104(c).

**Protocol Amendment: New Investigator**

If a principal investigator changes or another site is added:

1. ***New investigator****.* A Sponsor shall submit a protocol amendment when a new investigator is added to carry out a previously submitted protocol, except that a protocol amendment is not required when a licensed practitioner is added in the case of a treatment protocol under 312.34. Once the investigator is added to the study, the investigational drug may be shipped to the investigator and the investigator may begin participating in the study. The Sponsor shall notify FDA of the new investigator within 30 days of the investigator being added.

# Information Amendments

Information amendments may happen with greater frequency if the IND deals with a “home grown” drug or biologic. For example, there might be a significant change in a reagent because the one identified in the original application is no longer available.

Per [312.31](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.31)

1. ***Requirement for information amendment****.* A Sponsor shall report in an information amendment essential information on the IND that is not within the scope of a protocol amendment, IND safety reports, or annual report. Examples of information requiring an information amendment include:
	1. New toxicology, chemistry, or other technical information; or
	2. A report regarding the discontinuance of a clinical investigation.
2. ***Content and format of an information amendment.***An information amendment is required to bear prominent identification of its contents (e.g., "Information Amendment: Chemistry, Manufacturing, and Control", "Information Amendment: Pharmacology-Toxicology", "Information Amendment: Clinical"), and to contain the following:
	1. A statement of the nature and purpose of the amendment.
	2. An organized submission of the data in a format appropriate for scientific review.
	3. If the Sponsor desires FDA to comment on an information amendment, a request for such comment.
3. ***When submitted.***Information amendments to the IND should be submitted as necessary but, to the extent feasible, not more than every 30 days.

# How to submit an amendment to an existing IND

With any change to the IND, a new 1571 is required and is numbered sequentially. Additionally, the original (red binder) and two photocopies (grey binder) should be sent. These IND amendments should be sent to the assigned FDA project manager. Check the appropriate box for why the submission is being made (Section 11 of FDA Form 1571) and note also the following:

1. ***Content and format****.* A protocol amendment is required to be prominently identified as such (i.e., "Protocol Amendment: New Protocol", "Protocol Amendment: Change in Protocol", or "Protocol Amendment: New Investigator"), and to contain the following:

 (1)(i) In the case of a new protocol, a copy of the new protocol and a brief description of the most clinically significant differences between it and previous protocols.

* 1. In the case of a change in protocol, a brief description of the change and reference (date and number) to the submission that contained the protocol.
	2. In the case of a new investigator, the investigator's name, the qualifications to conduct the investigation, reference to the previously submitted protocol, and all additional information about the investigator's study as is required under 312.23(a)(6)(iii)(*b*).
1. Reference, if necessary, to specific technical information in the IND or in a concurrently submitted information amendment to the IND that the Sponsor relies on to support any clinically significant change in the new or amended protocol. If the reference is made to supporting information already in the IND, the Sponsor shall identify by name, reference number, volume, and page number the location of the information.
2. If the Sponsor desires FDA to comment on the submission, a request for such comment and the specific questions FDA's response should address.
3. ***When submitted****.* A Sponsor shall submit a protocol amendment for a new protocol or a change in protocol before its implementation\*. Protocol amendments to add a new investigator or to provide additional information about investigators may be grouped and submitted at 30-day intervals. When several submissions of new protocols or protocol changes are anticipated during a short period, the Sponsor is encouraged, to the extent feasible, to include these all in a single submission.

*\*In a private communication with the author, the FDA indicated that they do not have a timeline for reviewing protocol amendments, and that the investigator may continue the investigation under an amended protocol at their own discretion (after obtaining IRB approval). If the FDA has questions or concerns, the Sponsor will be contacted.*

# IND Safety Reports

### Safety reports can occur not only due to Serious Adverse Event occurrences, but also related to animal safety studies (for example, mice injected with the investigational agent and at the end of a year found a higher than expected incidence of tumors). Due to the importance that safety reporting is done as mandated, the text of 312.32 is below:

Sec. [312.32](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.32) **IND safety reports.**

1. ***Definitions.***The following definitions of terms apply to this section:

***Associated with the use of the drug.*** There is a reasonable possibility that the experience may have been caused by the drug.

***Disability.*** A substantial disruption of a person's ability to conduct normal life functions.

***Life-threatening adverse drug experience****.* Any adverse drug experience that places the patient or subject, in the view of the investigator, at immediate risk of death from the reaction as it occurred, i.e., it does not include a reaction that, had it occurred in a more severe form, might have caused death.

***Serious adverse drug experience***. Any adverse drug experience occurring at any dose that results in any of the following outcomes: Death, a life-threatening adverse drug experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse drug experience when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.

***Unexpected adverse drug experience***. Any adverse drug experience, the specificity or severity of which is not consistent with the current investigator brochure; or, if an investigator brochure is not required or available, the specificity or severity of which is not consistent with the risk information described in the general investigational plan or elsewhere in the current application, as amended. For example, under this definition, hepatic necrosis would be unexpected (by virtue of greater severity) if the investigator brochure only referred to elevated hepatic enzymes or hepatitis. Similarly, cerebral thromboembolism and cerebral vasculitis would be unexpected (by virtue of greater specificity) if the investigator brochure only listed cerebral vascular accidents. "Unexpected," as used in this definition, refers to an adverse drug experience that has not been previously observed (e.g., included in the investigator brochure) rather than from the perspective of such experience not being anticipated from the pharmacological properties of the pharmaceutical product.

1. ***Review of safety information.***The Sponsor shall promptly review all information relevant to the safety of the drug obtained or otherwise received by the Sponsor from any source, foreign or domestic, including information derived from any clinical or epidemiological investigations, animal investigations, commercial marketing experience, reports in the scientific literature, and unpublished scientific papers, as well as reports from foreign regulatory authorities that have not already been previously reported to the agency by the Sponsor.
2. ***IND safety reports***--(1) *Written reports*--(i) The Sponsor shall notify FDA and all participating investigators in a written IND safety report of:

#### Any adverse experience associated with the use of the drug that is both serious and unexpected; or

* 1. **Any finding from tests in laboratory animals** that suggests a significant risk for human subjects including reports of mutagenicity, teratogenicity, or carcinogenicity. Each notification shall be made as soon as possible and in no event later than 15 calendar days after the Sponsor's initial receipt of the information. Each written notification may be submitted on FDA Form 3500A or in a narrative format (foreign events may be submitted either on an FDA Form 3500A or, if preferred, on a CIOMS I form; reports from animal or epidemiological studies shall be submitted in a narrative format) and shall bear prominent identification of its contents, i.e., "IND Safety Report." Each written notification to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND. If FDA determines that additional data are needed, the agency may require further data to be submitted.

(ii) In each written IND safety report, the Sponsor shall identify all safety reports previously filed with the IND concerning a similar adverse experience, and shall analyze the significance of the adverse experience in light of the previous, similar reports.

1. *Telephone and facsimile transmission safety reports.* The Sponsor shall also notify FDA by telephone or by facsimile transmission of any unexpected fatal or life-threatening experience associated with the use of the drug as soon as possible but in **no event later than 7 calendar days after the Sponsor's initial receipt of the information**. Each telephone call or facsimile transmission to FDA shall be transmitted to the FDA new drug review division in the Center for Drug Evaluation and Research or the product review division in the Center for Biologics Evaluation and Research that has responsibility for review of the IND.
2. *Reporting format or frequency.* FDA may request a Sponsor to submit IND safety reports in a format or at a frequency different than that required under this paragraph. The Sponsor may also propose and adopt a different reporting format or frequency if the change is agreed to in advance by the director of the new drug review division in the CDER or the director of the products review division in the CBER which is responsible for review of the IND.
3. A Sponsor of a clinical study of a marketed drug is not required to make a safety report for any adverse experience associated with use of the drug that is not from the clinical study itself.

#### *Followup.* (1) The Sponsor shall promptly investigate all safety information it receives

1. Followup information to a safety report shall be submitted as soon as the relevant information is available.
2. If the results of a Sponsor's investigation show that an adverse drug experience not initially determined to be reportable under paragraph (c) of this section is so reportable, the Sponsor shall report such experience in a written safety report as soon as possible, but in no event later than 15 calendar days after the determination is made.
3. Results of a Sponsor's investigation of other safety information shall be submitted, as appropriate, in an information amendment or annual report.
4. ***Disclaimer.***A safety report or other information submitted by a Sponsor under this part (and any release by FDA of that report or information) does not necessarily reflect a conclusion by the Sponsor or FDA that the report or information constitutes an admission that the drug caused or contributed to an adverse experience. A Sponsor need not admit, and may deny, that the report or information submitted by the Sponsor constitutes an admission that the drug caused or contributed to an adverse experience.

Safety reports should be accompanied by FDA 3500A [MedWatch - Instructions for MedWatch 3500A](http://www.fda.gov/medwatch/report/instruc_10-25-05.htm). IND holders are mandated reporters, and will always fill out a FDA Form 3500A. FDA Form 3500 is for voluntary reporting, usually done by physicians or patients.

*Remember that FDA regulations about safety reporting and local IRB reporting are different. Refer also to local* [*IRB policy*](http://www.childrenshospital.org/~/media/research-and-innovation/office-of-clinical-investigation/62-unanticipated-problems-involving-risks-to-research-subjects-and-others-including-adverse-events102815.ashx?la=en) *for reporting of adverse events or unexpected problems.*

# Challenges of the Sponsor/Investigator

### Sponsors have many more obligations than just to the protocol itself. If considering a multi-site trial for which there is not sufficient infrastructure to oversee all the sites (Sponsors are responsible for the conduct of *all* sites), consider transferring some of the obligations to a contract research organization (CRO) [(312.52)](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.52). If considering utilizing a CRO, be prepared to pay for delegated study expenses in billable increments by the quarter hour. The Sponsor must also ensure that the study budget has the financial resources to support the CRO contract.

When working with a CRO, this adage also applies: “Responsibilities can be delegated, but NOT abdicated.” Any time responsibilities or tasks are delegated, whether to another individual or CRO, this must be done *in writing*.

Please keep in mind that working with the BCH Investigational Drug Service (IDS) Pharmacy or the ICCTR Monitoring services does not constitute delegating responsibilities to a CRO.

### The Sponsor of an IND has many responsibilities, including keeping watch over the trials to making sure that SAFETY remains the top priority. For Sponsor/investigator IND’s, this includes both policing oneself as an investigator and other investigators while overseeing overall trial safety and its risk vs. benefit ratio. Before initiating trials under an IND, consider the support available to the Sponsor/investigator through a regulatory affairs office to include initial staff education; proactive audits/monitoring; continuing education, and oversight of investigator conduct. Investigators who are jeopardizing the integrity of the trial or subject safety are the Sponsor’s responsibility, and must be dealt with accordingly.

# How are INDs Monitored?

There is much confusion between monitoring required by the FDA, and Data and Safety Monitoring by committees, also referred to as Data Safety Monitoring Boards (DSMBs). The purpose of Monitoring, as required by the FDA and further described here, is to assure adequate protection of the rights of human subjects, safety of all subjects, and the integrity of the resulting data submitted to the FDA. It is a *process that encompasses the entire study*:

* + Prior to the start of the study opening: provides for the education of study staff and verifying all mandated documentation and documentation procedures are in place.
	+ During the study: provides for continued training and education of the study staff; reviews the progress of the study; verifies that data collected is accurate.
	+ After the Study: verifies that all study visits are complete; drugs are accounted for; study data is valid; and regulation documents are complete and in the regulatory file.

### Data and Safety Monitoring Boards are a group of individuals with pertinent expertise who review, on a regular basis, data from ongoing clinical trials. The Board advises the Sponsor regarding the continuing safety of trial subjects as well as the continuing validity and scientific merit of the trial. More information can be found in the BCH [IRB policy](http://www.childrenshospital.org/~/media/research-and-innovation/office-of-clinical-investigation/513-data-and-safety-monitoring-plans102715.ashx?la=en). See also the FDA guidance document [“Establishment and Operation of Clinical Trial Data Monitoring Committees for Clinical Trial Sponsors”.](http://www.fda.gov/RegulatoryInformation/Guidances/ucm127069.htm)

*Remember that all of these activities are independent of one another; i.e. having a DSMB does not replace monitoring nor does having an audit on the protocol conducted.*

CFR [312.53](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.53) describes that a duty of a Sponsor is to select monitors. Beyond that, it says little. The FDA has a guidance document, “[Guideline for the Monitoring of Clinical Investigations”](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM269919.pdf) . Section 5.18 (bolded) of the ICH E6 Guidance Document (below) provides greater detail regarding monitoring.

ICCTR offers monitoring services for investigators who hold INDs. Please contact Lucinda Williams or Maggie Malsch for information, including a proposed monitoring plan and budget.

# Clinical Trials Database

Clinical trials conducted under an approved IND or IDE must use an electronic data capture (EDC) system that is compliant with FDA regulatory requirements ([21 CFR Part 11](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf)). Additional information is provided in the FDA Guidance for Industry supplements ([Computerized Systems used in Investigations](http://www.fda.gov/OHRMS/DOCKETS/98fr/04d-0440-gdl0002.pdf) and [Electronic Source Data in Clinical Investigations](http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM328691.pdf)). The software should have the technical controls in place to ensure data integrity as well as standard operating procedures (SOPs) for the maintenance of the EDC to ensure that regulatory and organizational policies are met.

1. **EDC Systems at BCH**

The Clinical Research Information Technology ([CRIT](http://web2.tch.harvard.edu/crit/index.html)) team hosts two electronic data capture systems at Boston Children’s Hospital (BCH):

· **REDCap** is a secure, web-based, user-friendly application for building and managing online or offline surveys and databases for research studies, quality improvement initiatives, and operational support. REDCap is not validated to be a 21 CFR Part 11 compliant solution at BCH; therefore, it cannot be used for FDA-regulated clinical trials.

*For more information, see the* [*REDCap website*](https://projectredcap.org/)*.*

· **Oracle Health Sciences InForm** is a comprehensive, integrated, open standards-based data capture and management platform. It has complete core data capture capabilities, including advanced query management, study design, real-time actionable visibility to data and source document verification (SDV).

*For more information, see the* [*Oracle Data Sheet*](http://www.oracle.com/us/industries/life-sciences/health-sciences-inform-ds-397109.pdf)*.*

Because Oracle Health Sciences InForm is HIPAA-certified and [21 CFR Part 11](http://www.fda.gov/downloads/RegulatoryInformation/Guidances/ucm125125.pdf) compliant, InForm is the electronic data capture and management platform used at BCH for clinical trials conducted under an approved IND or IDE.

1. **Project Setup / Development**

InForm trials are developed by the Clinical Research Informatics Team (CRIT) using the Oracle Health Sciences Central Designer application according to paper Case Report Forms provided by the study team. CRIT works closely with the trial’s project manager and statistician to design the trial and perform user acceptance testing (UAT). During this process, the study team should confirm all fields, forms, and events have been designed under the proper specifications. Additionally, edit checks should be created and tested to reduce data entry error while collecting live data. Generally, trials require about five months to deploy to production according to the timeline below.

Initial trial design and deployment 2-3 weeks

UAT / Trial design changes 2-4 months

Statistician & PI Approval 2-3 weeks

A request can be submitted through the CRIT website for the development of an InForm database.

1. **Requirements**
2. **Documents**

The following documents need to be provided to the CRIT developer assigned to the project:

* **Annotated Case Report Forms** are the most important tools for CRIT developers to design an InForm trial. They provide all the variables necessary to construct the trial and should include detailed specifications for each item.
	+ For all **continuous** data fields, the number of significant figures and units should be specified. It is also best practice to include minimum and maximum values to help the CRIT developer design edit checks for data validation.
	+ For all **multiple-choice** items, specify whether only one answer choice or multiple answers can be selected. Ensure the list of answer choices is exhaustive; otherwise *“Other”* should be included as an answer option.
	+ Paper CRFs should also indicate where **skip logic** should be included.
* The **Time and Events Schedule** provides the CRIT developer with the study-defined events and indicates the CRFs that are required at each event.
* During the design process, the study **Protocol** can be used by the CRIT developer to answer many design questions.
1. **End-User Training**

Each user that will need to access the InForm trial must have completed web-based user training. There are different training courses depending on the user’s role in the study. All users must complete the training for the specific version of InForm that is being used for the study database. BCH currently uses InForm v. 5.5. Requests for training (for both BCH internal users as well as external users) can be submitted through the CRIT website.

* **InForm GTM for Site Users** is required for Clinical Research Coordinators (CRCs) and Project Managers. Site users can enroll subjects into the trial, perform data entry, and prepare for monitoring visits.
* **InForm GTM for Sponsor Users** is required for Clinical Research Associates (CRAs) or Sponsors. Sponsor users can perform monitoring tasks and source document verification (SDV).
* **InForm GTM for PI Data Entry and Signature** is required for Principal Investigators. PIs are able to enroll subjects into the trial, enter data, and sign CRFs and case books.
1. **Data**

**Data Viewer**

The Data Viewer provides users with real-time actionable visibility into trial data. Users are able to instantly review and manage clinical trial data across visits and sites, filter data, and export data to Excel.

**Reporting Data Extracts (RDEs)**

Complete data extracts can be performed to extract the entire trial data into a zip file of SAS datasets. [Reporting Database Schema Guide](https://docs.oracle.com/cd/E55330_01/doc.610/E51803.pdf)

1. **InForm Trial Data Retention / Trial Close Out**

CRIT will keep the InForm trial accessible for 2.5 years after the study completion date (the last study visit). For the first 12 months, the study team will be able to complete the final data entry and cleanup procedures, and for the remaining 18 months, the team will have read-only access to the database.  At the end of the 2.5 year close-out period, the dataset will be archived, supporting any additional follow-up for regulatory or compliance reasons.

The close-out timelines can be further refined to accommodate needs of individual studies. Study teams should coordinate with CRIT team and the statistician for the study to make required adjustments. At this time, CRIT will perform a complete backup of the trial design and its data to be archived. The trial will be removed from the Oracle server.

# Clinical Trials Registration and Reporting

ClinicalTrials.gov is a Web-based resource that provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions. The website is maintained by the National Library of Medicine (NLM) at the National Institutes of Health (NIH).

This section provides an overview of who is responsible for the information entered, what studies should be registered, the reason for the creation of ClinicalTrials.gov, and the regulations. Some of the content in this section is taken directly from the ClinicalTrials.gov website (<http://clinicaltrials.gov>) and from the International Committee of Medical Journal Editors (ICJME) website (<http://icmje.org/about-icmje/faqs/clinical-trials-registration/>). Further information on the background can be found at <https://clinicaltrials.gov/ct2/about-site/background> and the history, policies and laws can be found at <https://clinicaltrials.gov/ct2/about-site/history>.

1. **Who is responsible for information in ClinicalTrials.gov?** Information on ClinicalTrials.gov is provided and updated by the Sponsor or principal investigator of the clinical study. Studies are generally submitted to the Web site (that is, registered) when they begin, and the information on the site is updated throughout the study. In some cases, results of the study are submitted after the study ends. This Web site and database of clinical studies is commonly referred to as a "registry and results database."
2. **What studies are in ClinicalTrials.gov?** ClinicalTrials.gov contains information about medical studies in human volunteers. Most of the records on ClinicalTrials.gov describe clinical trials (also called interventional studies). A clinical trial is a research study in which human volunteers are assigned to interventions (for example, a medical product, behavior, or procedure) based on a protocol and are then evaluated for effects on biomedical or health outcomes. ClinicalTrials.gov also contains records describing observational studies and programs providing access to investigational drugs outside of clinical trials (expanded access). ClinicalTrials.gov does not contain information about all the clinical studies conducted in the United States because not all studies are required by law to be registered (for example, observational studies and trials that do not study a drug, biologic, or device). See [FDAAA 801 Requirements](https://clinicaltrials.gov/ct2/manage-recs/fdaaa)  for more information. However, the rate of study registration has increased over time as more policies and laws requiring registration have been enacted and as more Sponsors and investigators have voluntarily registered their studies.
3. **What are the regulations governing ClinicalTrials.gov registration and reporting?**

Section 801 of the FDA Amendments Act [(FDAAA 801](https://clinicaltrials.gov/ct2/manage-recs/fdaaa)) covers the types of trials to be registered and the information to be submitted. In September 2016, HHS issued the final rule for Clinical Trials Registration and Results Information Submission ([42 CFR Part 11](https://www.federalregister.gov/documents/2016/09/21/2016-22129/clinical-trials-registration-and-results-information-submission)) clarifying and expanding the registration and results information submission requirements of FDAAA 801. This regulation took effect in January 2017. Applicable Clinical Trials (ACTs) under the FDA’s definition are required to be registered. Certain trials must also submit results data, including summary information on study participants and study outcomes, as well as adverse events. FDAAA 801 also established penalties for failing to register or submit the results of trials.

The International Committee of Medical Journal Editors (ICMJE) has developed a clinical trial [registration policy](http://icmje.org/news-and-editorials/update_2005.html) for papers submitted for publication, which has been adopted by over 1000 journals. This policy is detailed in a series of editorials (see [Updates and Editorials](http://icmje.org/news-and-editorials/) and [FAQs](http://icmje.org/about-icmje/faqs/)). Briefly, the ICMJE requires, and recommends that all medical journal editors require registration of clinical trials in a public trials registry at or before the time of first patient enrollment as a condition of consideration for publication. Editors requesting inclusion of their journal on the ICMJE website list of publications that follow ICMJE guidance should recognize that the listing implies enforcement by the journal of ICMJE’s trial registration policy. The ICMJE accepts registration in any registry that is a primary register of the WHO International Clinical Trials Registry Platform (ICTRP) or in ClinicalTrials.gov, which is a data provider to the WHO ICTRP.

In September 2016, NIH issued a [final policy](https://www.federalregister.gov/documents/2016/09/21/2016-22379/nih-policy-on-the-dissemination-of-nih-funded-clinical-trial-information) to promote broad and responsible dissemination of information from NIH-funded clinical trials through ClinicalTrials.gov. Under this policy, every clinical trial funded in whole or in part by NIH is expected to be registered on ClinicalTrials.gov and have summary results information submitted and posted in a timely manner, whether subject to FDAAA 801 or not. This policy is effective for applications for funding, including grants, other transactions, and contracts submitted on or after January 18, 2017. For the NIH intramural program, the policy applies to clinical trials initiated on or after January 18, 2017.

Form 3674

Form 3674 should be included with an IND/IDE application submitted to the FDA. This form is a certification of compliance under 42 U.S.C. § 282(j)(5)(B), with the requirements of ClinicalTrials.gov data bank (42 U.S.C. § 282(j)).

[Form 3674](https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM048364.pdf)

[Instructions](https://www.fda.gov/downloads/AboutFDA/ReportsManualsForms/Forms/UCM354618.pdf) for Form 3674:

Additional information:

1. FAQs can be found at <https://clinicaltrials.gov/ct2/manage-recs/faq>.
2. Training materials on registering and entering results into ClinicalTrials.gov (<https://clinicaltrials.gov/ct2/manage-recs/present#OverviewPolicies)>. This includes workshop slides on overview, registration and results overview, individual modules (participant, baseline, outcome measures, adverse events) as well as example studies for results data entry (parallel study, cross-over, dose-escalation, factorial, and multiple periods studies).

Timeline for ClinicalTrials.gov Reporting

|  |  |
| --- | --- |
| **Activity** | **Deadline** |
| Registration (FDA/NIH) | Within 21 days after enrollment of first participant |
| Registration (ICMJE) | Prior to enrollment of first participant |
| Update | No less than every 12 months |
| Recruitment status change | Within 30 days |
| Trial completion | Within 30 days |
| Results reporting | Within 12 months of primary completion date |

Boston Children’s Hospital Resources

For assistance with ClinicalTrials.gov registration and reporting, please contact the following individuals:

Lauren Robertson and Lindsey Rice, Research Administration – BCHClinicalTrials.gov@childrens.harvard.edu

Edie Weller, Director, ICCTR Biostatistics – Edie.Weller@childrens.harvard.edu

The table below summarizes useful resource documents available either at the ClinicalTrials.gov or on the BCH research administration website.

|  |  |  |  |
| --- | --- | --- | --- |
| **Purpose**  | **Description** | **Filename**  | **Author** |
| Provide investigators with overview of the intent and scope of regulations, timelines and investigator responsibilities for ClinicalTrials.gov information.  | Summary of the history and regulatory requirements.  |  ClinicalTrials.gov Overview Power Point (on BCH Clinical Research website under [ClinicalTrials.gov](http://web2.tch.harvard.edu/research/mainpageS2732P59.html) section) | BCH Assistant Director of Research Administration |
| Help investigators determine if trial is an applicable clinical trial (ACT).  | The final rule for Clinical Trials Registration and Results Information Submission (42 CFR Part 11) specifies requirements for submitting clinical trial information to ClinicalTrials.gov. The “Checklist for Evaluating Whether a Clinical Trial or Study is an Applicable Clinical Trial (ACT)” (or “ACT Checklist”) and this elaboration is intended to assist users in evaluating whether a clinical trial or study is considered to meet the definition of an ACT, as specified in 42 CFR 11.22(b), and is subject to “expanded” registration requirements under the final rule. | <https://prsinfo.clinicaltrials.gov/ACT_Checklist.pdf>  | ClinicalTrials.gov |
| Additional information on the definitions of response party and applicable clinical trial  | The elaboration of definitions of “Responsible Party” and “Applicable Clinical Trial” represent the National Institutes of Health's (NIH's) current thinking on this topic. Definitions” in the subject line. | <https://prsinfo.clinicaltrials.gov/ElaborationsOnDefinitions.pdf> | ClinicalTrials.gov |
| Define the trials which must be registered and have results submitted to ClinicalTrials.gov.  | Provide overview of the trials that are required to be entered into clinical trials.gov, timelines, definitions of interventional vs. observational, and Sponsor/responsible party information | ClinicalTrials.gov Tip Sheet (on BCH Clinical Research website under [ClinicalTrials.gov](http://web2.tch.harvard.edu/research/mainpageS2732P59.html) section) | BCH Assistant Director of Research Administration |
| Describe how the protocol information entered into the system is reviewed by ClinicalTrials.gov staff.  | ClinicalTrials.gov reviews protocol information for apparent validity, meaningful entries, logic and internal consistency, and formatting. This document is intended to assist data providers in preparing registration records by providing an overview of ClinicalTrials.gov review criteria. | <https://prsinfo.clinicaltrials.gov/ProtocolDetailedReviewItems.pdf> | ClinicalTrials.gov |
| Provide overview of the data elements that are entered into the ClinicalTrials.gov system.  | ClinicalTrials.gov Protocol Data Element Definitions (DRAFT). The document at this link describes the definitions for protocol registration data elements submitted to ClinicalTrials.gov for interventional studies (clinical trials) and observational studies. | <http://prsinfo.ClinicalTrials.gov/definitions.html>.  | ClinicalTrials.gov |
| Describe how the protocol results that are entered into the system is reviewed by ClinicalTrials.gov staff.  | ClinicalTrials.gov staff reviews protocol and results information. The review focuses on assessing whether the entered data could be understood by a reader of the medical literature who is not already familiar with the study. This document is intended to assist data providers in preparing results records by providing an overview of ClinicalTrials.gov review criteria. This document is not comprehensive. Additional explanatory user documents are also available at http://prsinfo.ClinicalTrials.gov/fdaaa.html. | <https://prsinfo.clinicaltrials.gov/ResultsDetailedReviewItems.pdf> | ClinicalTrials.gov |
| Provide detailed documentation on using the system (called the Protocol Registration System (PRS)).  | The ClinicalTrials.gov Protocol Registration and Results System (PRS) is a web-based tool used to submit clinical study information to ClinicalTrials.gov. Records submitted through the PRS are available to the public at ClinicalTrials.gov. This document describes how to use the PRS and provides step-by-step instructions for PRS functions. Document sections describe steps to posting a study record on ClinicalTrials.gov, account information, creating new records and entering data, preparing, approving, releasing a record to the system, review process, updating and maintaining records, handle problems, uploading/downloading files and application program interface. | PRS User's Guide (on BCH Clinical Research website under [ClinicalTrials.gov](http://web2.tch.harvard.edu/research/mainpageS2732P59.html) section) | ClinicalTrials.gov |
| Describe how to register trial in ClinicalTrials.gov | This file provides details about interfacing with the ClinicalTrials.gov Protocol Registration and Results System when registering a trial. **Recommended resource for learning how to use the system.**  | How to Register your Trial Power Point (on BCH Clinical Research website)<https://catalyst.harvard.edu/pdf/regulatory/CTGOV_HOWTOREG.pdf> | Clinical and Translational ScienceAward organizations and the NationalLibrary of Medicine.  |
| Describe how to enter results from trial into ClinicalTrials.gov | This file provides details about interfacing with the ClinicalTrials.gov Protocol Registration and Results System when entering data and results from a trial. **Recommended resource for learning how to use the system.** | Results Reporting Power Point (on BCH Clinical Research website under [ClinicalTrials.gov](http://web2.tch.harvard.edu/research/mainpageS2732P59.html) section) | Clinical and Translational ScienceAward organizations and the NationalLibrary of Medicine.  |

# Appendices

* 1. **IND Application Template**

[Download the current forms](http://www.fda.gov/opacom/morechoices/fdaforms/cder.html) FDA 1571 and 1572

[Completing the form 1571](http://www.fda.gov/cber/ind/1571instr.htm)

**IND Submission Template**

# Forms FDA 1571

*Completed Form FDA 1571 should be referenced here.*

A completed, signed Form FDA 1571 is included with this submission.

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# Introductory statement and general investigational plan

## 3.1 Introductory Statement

*This section is brief; usually 2-3 pages should be sufficient. This section should contain information about the clinical indication and the reason that you think the product has a place in the treatment of these patients. The FDA is concerned primarily with safety of the participants of your study, so the scientific merit of the study does not have to be explored in depth in this section. It is best to state briefly why you believe this study is necessary and who will benefit from the study, then go into some more detail as to how the participants in the study are to be protected.*

 *After your introductory statement, use the headings below to ensure you fulfill all of the requirements.* ***Maintain all of the headings*** *in this document and if not applicable to your IND, simply state this.*

### **3.1.1 Name of the Drug and All Active Ingredients**

### **3.1.2 Pharmacological Class of the Drug**

### **3.1.3 Structural Formula of the Drug**

### **3.1.4 Formulation of the Dosage Forms to be Used**

### **3.1.5 Route of Administration**

### **3.1.6 Objectives and Duration of the Proposed Clinical Investigation(s)**

*State the primary and secondary objectives of the clinical trial, and state the duration of the proposed study, from the completed protocol.*

## 3.2 Summary of Previous Human Experience

*This is a brief summary of previous human experience with the drug(s), with reference to the literature or other INDs if pertinent. Also, investigational or marketing experience in other countries may be relevant to the safety of the proposed clinical investigation(s). This topic will be written up in detail in Section 8. However, for many Sponsor-Investigator INDs that use commercially available drugs, Section 2.2 and 8 are often identical.*

## 3.3 Status of Drug in Other Countries

*If the drug has been withdrawn from investigation or marketing in any country for any reason related to safety or effectiveness, identification of the country(ies) where the drug was withdrawn and the reasons for the withdrawal are stated here. For a Sponsor-Investigator IND, you may simply state you are not aware of any withdrawals.*

##

## 3.4 General Investigational Plan

## 3.5 Rationale

*State here the rationale for the research study planned. Briefly refer to the non-clinical data supporting the rationale if relevant. The bulk of the non-clinical data (e.g., animal models, in vitro models, etc.) should be provided in the Pharmacology Section (Section 7). This section should be brief, one to two pages at most.*

## 3.6 Indication(s) to be Studied

*This should be different from the indication the drug is already approved for.*

## 3.7 General Approach for Evaluation of Treatment

*State here the sequence of studies planned or a general description of the population to be studied.*

## 3.8 Description of First Year Trial(s)

*Briefly describe what kind of clinical study design you will use in the first year of the trial. If plans are not developed for the entire year, the Sponsor should so indicate.*

### **3.8.1 Number of Subjects to be Evaluated**

###

### **3.8.2 Drug Related Risks**

*Any risks of particular severity or seriousness anticipated on the basis of the toxicological data in animals or prior studies in humans with the drug(s) or related drugs.*

### **RESERVED**

# Investigator Brochure

*For Sponsor-Investigator initiated INDs of approved products, there is no requirement to produce an Investigator Brochure. You can incorporate the following statement:*

In accordance with 21 CFR Part 312.55(a), an Investigator’s Brochure is not required for a Sponsor-Investigator IND.

*However, it is appropriate here to refer to the labeling and provide a URL link to the most current product label. You may find these links useful for finding current product labeling:*

* [*http://dailymed.nlm.nih.gov/dailymed/about.cfm*](http://dailymed.nlm.nih.gov/dailymed/about.cfm)
* [*http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/*](http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/)

*You may also reference Letters of Authorization in this section if you are receiving product directly from the manufacturer.*

*Note: For multi-center studies, an Investigator-Brochure is required.*

# Protocol

## 6.1 Study Protocol

*The complete clinical protocol for this clinical study can be included in the body of the IND or attached as an appendix to this IND, and referenced here* *as Appendix (x). Also, state here where the study is to take place and give the name and address of the Institutional Review Board responsible for the initial and continuing review and approval of the study.*

A copy of the clinical protocol is provided with this submission.

## 6.2 Informed Consent

*If the investigation involves an exception from informed consent under 21 CFR 50.24, the Sponsor shall prominently identify on Form FDA 1571 and here that the investigation is subject to the requirements in 21 CFR 50.24. Otherwise it must be stated here that informed consent will be obtained by the participants of the study in accordance with 21 CFR Part 50 Protection of Human Subjects.*

A copy of the informed consent document is provided with this submission.

## 6.3 Investigator and Facilities Data

*Attach FDA Form 1572 and CV of the principal investigator(s) as two appendixes, and reference those appendixes here. Actually, you are not required to submit form 1572 to the FDA. However, it is the easiest way to collect all the information that must be submitted under 21 CFR 312.23(a)(6)(iii)(b). The alternative is to submit the information as a narrative, but we highly recommend using the form.*

A Form FDA 1572 and a copy of the Sponsor-Investigator and Study PI’s CV are provided with this submission.

Forms FDA 3674 and 3454 *[if applicable]* are also provided with this submission.

# Chemistry, Manufacturing and Control Information

*If the investigational drug has been marketed, this section may be covered by referring to the product labeling. You may refer back to the URL identified in Section 4. Alternatively, it might be appropriate to refer to a ‘Letter of Authorization’ referenced in Section 9 of Form FDA 1571 if using a drug provided by a commercial company.*

Dose Level

Lot Number

## 7.1 Environmental Assessment

*Insert the statement below, unless there is a reason to believe the distribution and use of the drug could have an environmental impact.*

We request a claim for categorical exclusion for this proposed clinical trial as provided for in 21 CFR Part 312.31(e) in that the drug shipped under this notice is intended to be used in clinical trials in which the amount of waste expected to enter the environment may reasonably be expected to be non-toxic.

# Pharmacology and Toxicology Information

## 8.1 Pharmacology and Drug Distribution

*This section should contain any non-clinical data supporting the rationale for the proposed study. This may be animal models of disease, cell-based models, or other supporting information. Depending on the importance of this information to your proposal you should consider how detailed the information should be. Always provide published literature supporting the claims.*

*If you are proposing a new route of administration for an approved drug be aware that FDA may require additional toxicology studies to be conducted. This should be discussed with FDA prior to submitting the IND.*

 *As was true for Section 6, you may use an authorization letter(s) or cite the drug label to satisfy this section.*

# Previous Human Experience

*Provide a summary of known use of the product. If the drug(s) is already marketed in the US, then you may be able to simply refer to the product labeling. Some guidelines are listed below:*

1. *If the drug has been investigated or marketed previously, either in the United States or other countries, detailed information about such experience that is relevant to the safety of the proposed investigation or to the investigation’s rationale.*
2. *If the drug has been the subject of controlled trials that are not discussed in the product label, and are relevant to the proposed study, they should be summarized in this section. It is recommended to summarize the available clinical information in tabular form to ensure that reviewers can easily identify relevant studies. An example of a table format is provided below. Any published material that is relevant to the safety of the proposed investigation or to an assessment of the drug’s effectiveness for its proposed investigational use should be provided in full. Published material that is less directly relevant may be supplied by a bibliography.*
3. *If the drug is a combination of drugs previously investigated or marketed, the information should be provided for each active drug component. However, if any component in such combination is subject to an approved marketing application or is otherwise lawfully marketed in the United States, the Sponsor is not required to submit published material concerning that active drug component unless such material relates directly to the proposed investigational use (including publications relevant to component- component interaction).*
4. *If the drug(s) has been marketed outside the United States, a list of the countries in which the drug has been marketed and a list of the countries in which the drug has been withdrawn from marketing for reasons potentially related to safety or effectiveness.*

### **Table 1. Example of Data Summary Table**

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Study(Reference) | N (age range, years) | Treatment | Doses Administered | Outcome Measures | Reported Adverse EventsN (%) |
| Name (Bibliography) |  |  |  |  |  |
|  |  |  |  |  |  |

#

# Additional Information

*In certain applications, as described below, information on special topics may be needed. Such information shall be submitted in this section as outlined below. Otherwise you may simply state ‘not applicable’. This could include specific information requested by FDA following a pre-IND meeting.*

## 10.1 Drug Dependence and Abuse Potential

*If the drug is a psychotropic substance or otherwise has abuse potential, a section describing relevant clinical studies and experience and studies in test animals.*

## 10.2 Radioactive Drugs

*If the drug is a radioactive drug, sufficient data from animal or human studies should be provided, to allow a reasonable calculation of radiation-absorbed dose to the whole body and critical organs upon administration to a human subject. Phase 1 studies of radioactive drugs must include studies which will obtain sufficient data for dosimetry calculations.*

## 10.3 Pediatric Studies

*If the investigational drug will be studied in pediatric setting, plans for assessing pediatric safety and effectiveness should be provided.*

## 10.4 Other Information

*A brief statement of any other information that would aid evaluation of the proposed clinical investigations with respect to their safety or their design and potential as controlled clinical trials to support marketing of the drug.*

## 10.5 Selected References

*If you are including reprints with your submission, list them in this section.*

# Relevant Information

*If requested by FDA, any other relevant information needed for review of the application.*

**List of References**

**B. Pre-IND Meeting Request Template**

In addition to an FDA Form 1571, the meeting request should include the following information:

1. Product name and application number (if applicable).
2. Chemical name and structure.
3. Proposed indication(s).
4. The type of meeting being requested (i.e., Type A, Type B, or Type C).
5. A brief statement of the purpose of the meeting. This statement could include a discussion of the types of completed or planned studies or data that the Sponsor or applicant intends to discuss at the meeting, the general nature of the critical questions to be asked, and where the meeting fits in overall development plans.
6. A list of the specific objectives/outcomes expected from the meeting.
7. A preliminary proposed agenda, including estimated amounts of time needed for each agenda item and designated speaker(s).
8. A draft list of specific questions, grouped by discipline.
9. A list of all individuals (including titles) who will attend the proposed meeting from the Sponsor's organization and consultants.
10. A list of Agency staff requested by the Sponsor or applicant to participate in the proposed meeting. If a Sponsor or applicant is not sure which Agency officials should attend the meeting, the applicant does not need to include specific individuals in the request, but should include requested disciplines, if known.
11. The approximate date on which supporting documentation will be sent to the review division.
12. Suggested dates and times (i.e., morning or afternoon) for the meeting. (Provide to the FDA 3 or 4 options of dates and times that the Sponsor and the Sponsor’s team are available to meet.)

**C. Pre-IND Meeting Information Package Template**

1. Product name and application number (if applicable).
2. Chemical name and structure.
3. Proposed indication(s).
4. Dosage form, route of administration, and dosing regimen (frequency and duration).
5. A brief statement of the purpose of the meeting. This statement could include a discussion of the types of completed or planned studies or data that the Sponsor or applicant intends to discuss at the meeting, the general nature of the critical questions to be asked, and where the meeting fits in overall development plans.
6. A list of the specific objectives/outcomes expected from the meeting.
7. A proposed agenda, including estimated amounts of time needed for each agenda item and designated speaker(s).
8. A list of specific questions grouped by discipline.
9. Clinical data summary (as appropriate).
10. Preclinical data summary (as appropriate).
11. Chemistry, manufacturing, and controls information (as appropriate).

Although CDER and CBER also request the information listed in items 1 - 8 above in the request for a formal meeting, these items should be updated in the information package to reflect the most current and accurate information available to the Sponsor. If a Sponsor wishes specific guidance regarding the contents of the information package, they should contact the project management staff assigned to the submission. If the product is in the early stages of development and no project manager has been assigned, the Sponsor or applicant should contact the appropriate Chief, project management staff in CDER or the applications division in the CBER office with product responsibility.

**D. IND Annual Report Template**

**For each individual study under the IND**

Summary of study status

* Title and identifier
* Purpose
* Patient population
* Statement if study is completed

Table including the following

* Number of subjects planned for inclusion
* Number of subjects entered to date
* Age group, gender, race

### Number completed

* Number dropped out

Study completed or interim results Description of study results

**IND Summary Information for the previous year (clinical & non-clinical)**

A narrative or tabular summary showing the most frequent and most serious adverse experiences by body system.

A summary of all IND safety reports submitted during the past year.

A list of subjects who died during participation in the investigation, with the cause of death for each subject.

A list of subjects who dropped out during the course of the investigation in association with any adverse experience, whether or not thought to be drug related.

A brief description of what, if anything, was obtained that is pertinent to an understanding of the drug’s actions, including, for example, information about dose response, information from controlled trials, and information about bioavailability.

A list of the preclinical studies (including animal studies) completed or in progress during the past year and a summary of the major preclinical findings.

A summary of any significant manufacturing or microbiological changes made during the past year.

A description of the general investigational plan for the coming year to replace that submitted 1 year earlier.

A description of any protocol modifications made during the previous year and not previously reported to the IND in a protocol amendment.

Sample Study Summary:

* **Study Title:** Effects of XXX drug on vascular function in children. (Protocol ID ABC123)
* **Study Purpose:** To assess the acute (0-2 hours) effects of XXX drug on vascular endothelial function in children.
* **Study Population:** Healthy male and female children ages 10-14 years
* **Study Status:** Enrollment has ended.
* **Number of Subjects Planned for Inclusion:** 60
* **Number Entered to Date by Age:** 8 yrs = 3; 9 yrs = 9; 10 yrs = 3; 11 yrs = 7; 12 yrs = 5; 13 yrs = 2; 14 yrs = 6
* **Number Entered to Date by Gender:** Males = 16; Females = 19
* **Number Entered to Date by Race:** White = 30; African American = 5; Asian = 0; Native American = 0
* **Number of Subjects Who Completed Study:** 35
* **Number of Subjects Who Dropped-out:** 0
* **Study Summary:** Preliminary data suggests that neither overweight nor normal weight children experience vascular dysfunction following ingestion of XXX drug. Further enrollment is necessary to confirm this finding.
* **Role of Drug in the Study:** QQQ drug is an important component of the overall vascular function technique. Quantifying the dilation effects of the drug provides information concerning vascular smooth muscle function, which is an endothelium-independent phenomenon.
* **Drug Dosage:** One dose of XXX drug and QQQ drug tablet will be administered to each study participant.
* **Drug Safety Data:** No new safety information for XXX drug or QQQ drug has been gleaned from this study.
* **Drug Protocol Monitoring:** A pediatric cardiologist, Dr. Jones, supervises the XXX drug and QQQ drug protocol. In addition, Dr. Smith, a pediatrician, serves as a sub-investigator for the proposed study.

### Sample IND Summary Information for the previous year (clinical & non clinical)

**Summary Information for Serious Adverse Events:** No serious adverse events have occurred. The most common complaint has been mild headache, which has occurred in approximately half of subjects. All headaches dissipated within 15 minutes of onset. No IND safety reports were submitted during the past year. No subjects died during participation. No subject dropped-out of the study for any reason. It seems that QQQ drug’s action causes short-term mild headache in children ages 8-14. No other symptoms have been observed to date.

**Pre-clinical**

No animal studies were conducted in conjunction with this trial.

**Manufacturing Changes**

Drugs XXX and QQQ are marketed drugs obtained from their respective manufacturers. No changes to the formulations have taken place.

**Investigational Plan for Coming Year**

A protocol to assess the effects of weight-loss on vascular function in obese children was submitted February 22, 2008, serial 005.

**Protocol Modifications**

Subjects are no longer being enrolled into this study under this protocol.

### **Sample Cover Letter for IND Annual Report**

Food and Drug Administration

Center for Drug Evaluation and Research Division of Cardio-Renal Drug Products, HFD-110 Attention: Division Document Room, 5002

1451 Rockville Pike

Rockville, MD 20852

March 13, 2008

Re: IND 12345, Serial 006

XXX drug and QQQ drug

IND Annual Report

To Whom It May Concern:

Enclosed are three copies (original and 2 photocopies) of Form FDA 1571 and IND Annual

Report for IND 12345, XXX drug and QQQ drug, covering the time frame of 3/07 to 2/08.

Thank you for incorporating this Annual Report into my IND file.

Sincerely,

Donna D. Doktor, MD Associate Professor

# Reference Regulations

### Code of Federal Regulations:

[312.50](http://google2.fda.gov/search?client=FDA&amp;site=FDA&amp;lr&amp;proxystylesheet=FDA&amp;output=xml_no_dtd&amp;getfields=%2A&amp;q=312.50&amp;as=GO): Defines general responsibilities of Sponsors

[312.52](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.52): Describes transferring duties to a CRO

[312.55](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.55): Keeping investigators informed of new observations with respect to adverse effects and safe use

[312.58](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.58): Inspection of Sponsor’s records and reports

[312.59](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.59): Disposition of unused supply of investigational drug

[312.60](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.60): General responsibilities of investigators

[312.61](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.61): Control of the investigational drug

[312.64](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.64): Investigator reports

### [312.66](http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=312.66): Assurance of IRB review

* 1. : Inspection of investigators records and reports
	2. : Handling of controlled substances
	3. : Disqualification of a clinical investigator