SPONSOR-INVESTIGATOR TRAINING: MODULE 1

IND/IDE Support Program

April 23, 2020

Children's Hospital of Philadelphia®

OVERVIEW

- Introduction to Investigational New Drug Application (IND) and IND Sponsorship
- Regulatory Requirements of an IND Application
- IND Determinations: What to expect from the FDA
- Clinical Holds
- Resources
- References (please also see supplement packet)

INTRODUCTION TO THE IND

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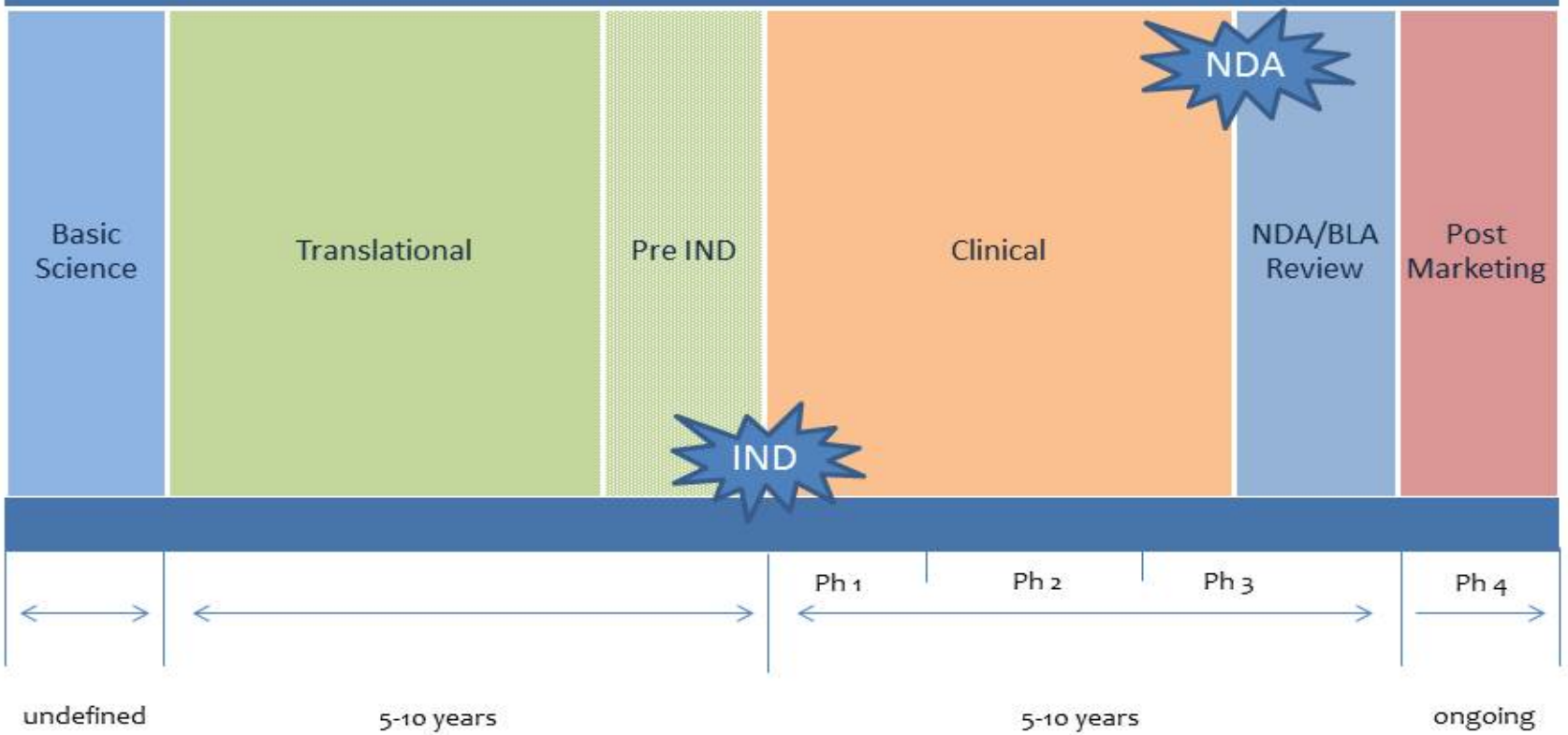
Drug Development Overview



Source FDA Pediatric Conference 9/2014

FDA Terms

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CLINICAL TRIAL PHASES

Phase	# Patients	Purpose
1/Pilot	Less than 100	• First in human, first in children • Safety/side effects • How is the drug metabolized • PK/PD, Dose finding
2	100s	• Preliminary efficacy endpoints • Short term side effects
3	100s-1000s	• Primarily an efficacy trial • Effectiveness and safety as it pertains to the risk/benefit profile of the drug • Multi-site

Note: some phases can be combined

AN IND MIGHT BE NEEDED IF…

- The population being studied (i.e. children) is not listed in the FDA label for that indication
- The drug is not approved for marketing in the US
  - For example, the drug is only approved in another country, is in development in the US, or is a supplement or food not approved for marketing as a drug
- The drug is approved for a use other than the proposed use
  - If the investigation involves a route of administration, dose, patient population, or other factor that significantly increases the risk (or decreases the acceptability of the risk) associated with the use of the drug product (21 CFR 312.2 (b) (1) (iii))
- The study will support labeling of the drug
  - If the study is intended to be reported to the FDA as a well-controlled study in support of a new indication or any other significant change in the labeling of the drug

PRE-IND MEETINGS

- A sponsor/sponsor-investigator can reach out to the FDA about their proposed study (prior to submitting an IND application) by scheduling a Pre-IND Meeting
- This might be advantageous in cases when:
  - They are unsure if their study would need to be under an IND
  - The Sponsor would like prescriptive feedback from the FDA they can incorporate into the proposed protocol
  - There is a novel indication or the drug itself is a new molecular entity
  - There are aspects of the study drug (ex: pharmacology, toxicology), that the FDA might be more knowledgeable about
- This meeting can be in-person, via teleconference, or in-writing
- Please see attached supplement for additional information

EXPANDED ACCESS INDS

- An expanded access IND for a drug, primarily conducted for treatment
- There are a few different types of expanded access INDs:
  - Expanded access for widespread use
  - Expanded access for intermediate-size patient populations
  - Expanded access for individual patients
    - Single patient IND (sIND)
    - Single patient 'Emergency Use' IND (eIND)
- Sometimes referred to as "Compassionate use"
- The drug used may be an investigational drug OR a lawfully marketed drug

CRITERIA FOR A SINGLE SUBJECT IND

- Serious or immediately life-threatening disease or condition
- No comparable or satisfactory alternative therapy to diagnose, monitor or treat the disease or condition
- The potential patient benefit justifies the potential risks of the treatment use, and the risks are not unreasonable in the context of the disease or condition
- The sIND will not interfere with the initiation, conduct or completion of clinical investigations that could support marketing approval or compromise development of the expanded access use

Note: FDA & IRB must approve or concur of the use of the drug prior to administration, and there is adequate time for both to do so

CRITERIA FOR AN EMERGENCY IND

- A life-threatening or severely debilitating situation
  - High likelihood of death
  - Major and irreversible morbidity
- No standard acceptable treatment available
- No comparable or satisfactory alternative therapy
- Patient may benefit from use of an investigational drug **BUT**
  - Patient does not meet the criteria of an existing study protocol, or
  - Approved study protocol does not exist
- Insufficient time to obtain IRB approval
  - Need for investigational drug does not allow time for submission/review and approval by IRB (Sponsor should still contact IRB, and the IRB will let them know if there is enough time to review)
  - Need for investigational drug also does not allow time for submission to FDA in the usual manner

INDS AS CLINICAL INVESTIGATIONS

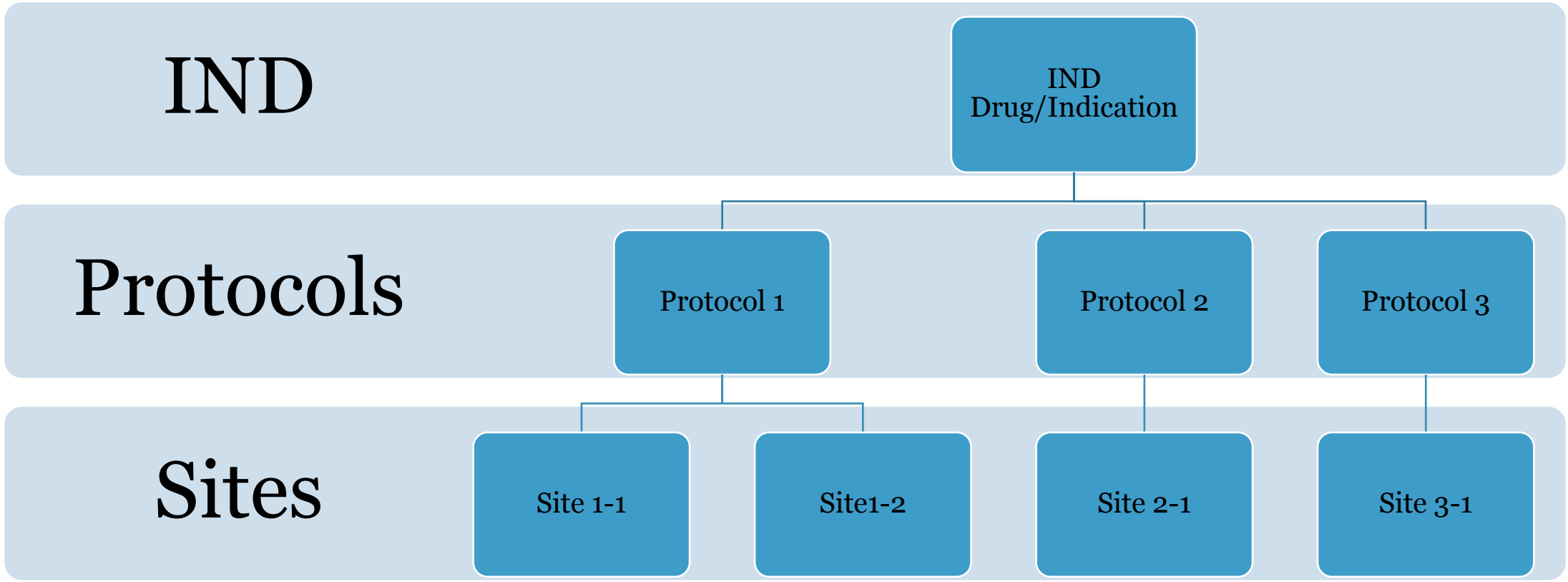
- Investigators are looking to study the use of a medication as part of a clinical investigation
- Primary goal is assessing product safety and effectiveness
- Data that is generated for publication in academia, and product development in industry
- Can be any phase (I, II, III, or IV)

IND GOALS AND REQUIREMENTS

- Clinical Development Goals:
  - Generate data to…
    - Establish that the drug will not expose humans to unreasonable risks
    - Establish that the product is effective
    - Provide basis for labeling change
    - Provide basis for marketing the product

- Requirements:
  - A sponsor shall submit an IND to FDA if the sponsor intends to conduct a clinical investigation with an investigational new drug that is subject to 312.2(a).
  - A sponsor shall not begin a clinical investigation subject to 312.2(a) until the investigation is subject to an IND which is in effect in accordance with 312.40.

IND PROTOCOL AND SITES



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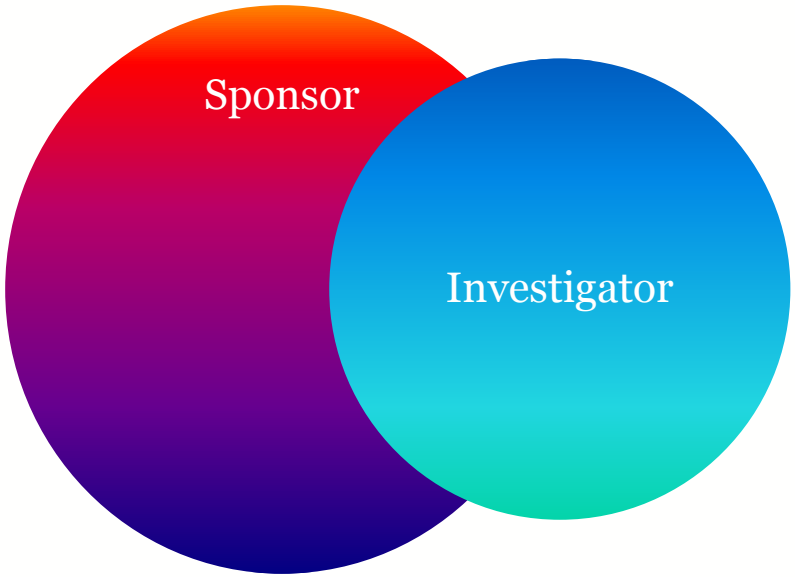
INTRODUCTION TO IND SPONSORSHIP

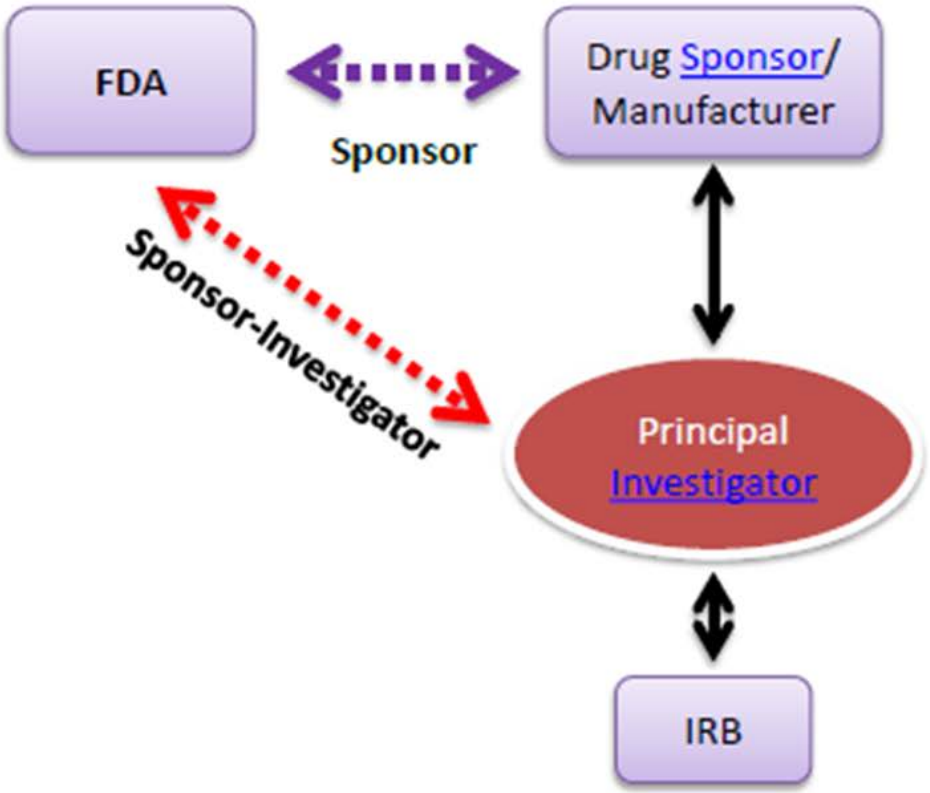
SPONSOR AND INVESTIGATOR RESPONSIBILITIES

Sponsor and Investigator Separated Responsibility



Sponsor-Investigator Compounded Responsibility

COMMUNICATION WITH THE FDA



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REGULATORY REQUIREMENTS AND FORMAT OF AN INVESTIGATIONAL NEW DRUG APPLICATION

GENERAL PRINCIPLES OF THE IND SUBMISSION (21 CFR 312.22)

- FDA's Primary Objectives
  - Assure **safety** and **rights of subjects**, and **quality of the scientific evaluation** is adequate to evaluate the drug's **effectiveness and safety** for market approval
- Focus of initial IND submission
  - General investigational plan
  - Protocols for specific human studies
  - Novelty and developmental phase of the drug
  - The extent to which the study drug has been studied previously
  - The known or suspected risks

IND APPLICATION

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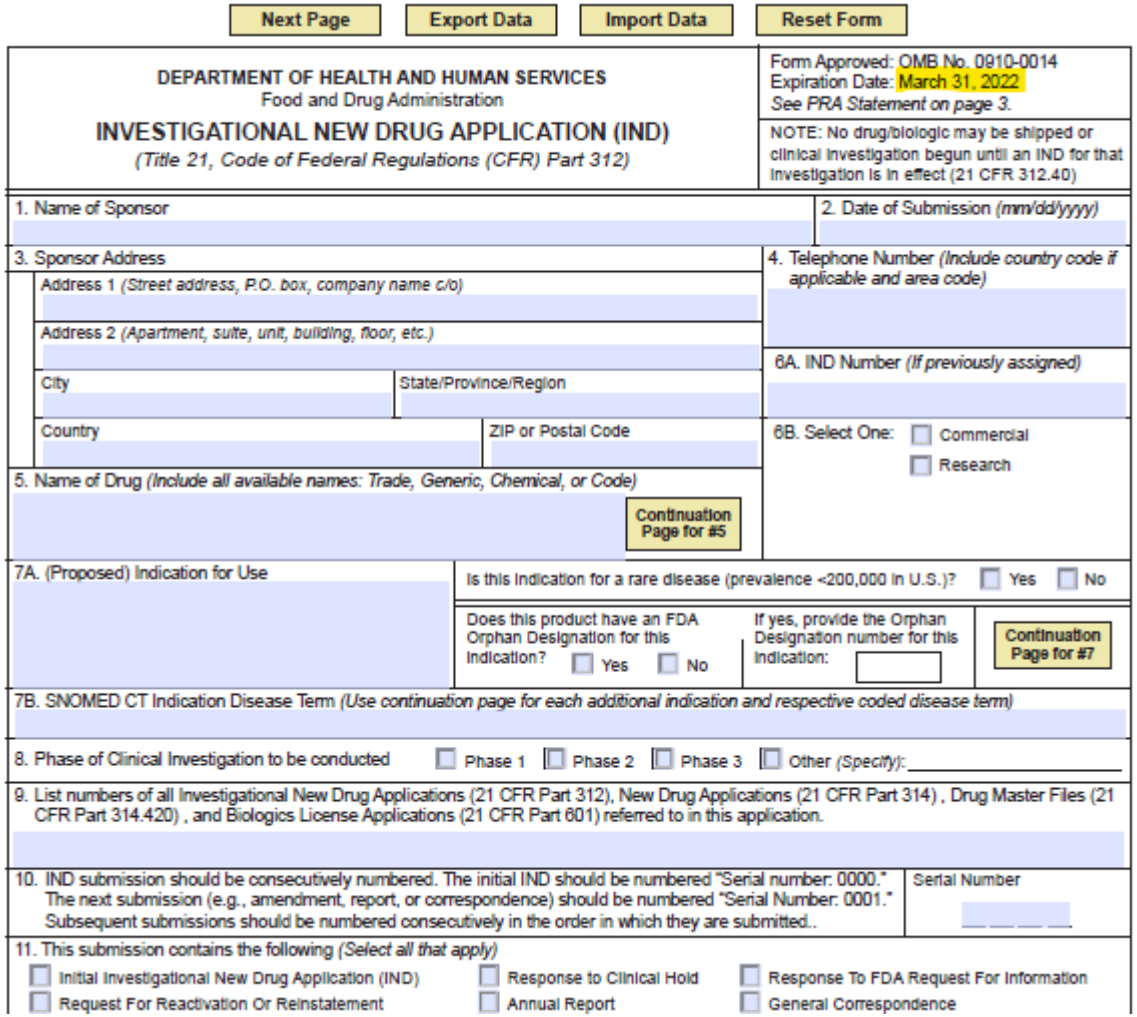
ORDER OF IND APPLICATION

- Coversheet (Form FDA 1571)
- Table of Contents
- Introductory Statement and General Investigational Plan
- Previous Human Experience with the Investigational Drug
- Investigator's Brochure
- Protocol
- Chemistry, Manufacturing, and Control Information
- Pharmacology and Toxicology Information
- Additional Information

SECTION 1: FDA FORM 1571

- In addition to being a cover sheet for the submission, this is also where the Sponsor agrees to conduct research according to FDA regulations



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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

INVESTIGATIONAL NEW DRUG APPLICATION (IND)
(Title 21, Code of Federal Regulations (CFR) Part 312)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See PRA Statement on page 3.

NOTE: No drug/biologic may be shipped or clinical investigation begun until an IND for that investigation is in effect (21 CFR 312.40)

1. Name of Sponsor
2. Date of Submission *(mm/dd/yyyy)*
3. Sponsor Address
   - Address 1 *(Street address, P.O. box, company name c/o)*
   - Address 2 *(Apartment, suite, unit, building, floor, etc.)*
   - City
   - State/Province/Region
   - Country
   - ZIP or Postal Code
4. Telephone Number *(Include country code if applicable and area code)*
5. Name of Drug *(Include all available names: Trade, Generic, Chemical, or Code)*
   Continuation Page for #5
6A. IND Number *(If previously assigned)*
6B. Select One: ☐ Commercial ☐ Research
7A. (Proposed) Indication for Use
Is this indication for a rare disease (prevalence <200,000 in U.S.)? ☐ Yes ☐ No
Does this product have an FDA Orphan Designation for this indication? ☐ Yes ☐ No
If yes, provide the Orphan Designation number for this indication:
Continuation Page for #7
7B. SNOMED CT Indication Disease Term *(Use continuation page for each additional indication and respective coded disease term)*
8. Phase of Clinical Investigation to be conducted ☐ Phase 1 ☐ Phase 2 ☐ Phase 3 ☐ Other *(Specify)*:
9. List numbers of all Investigational New Drug Applications (21 CFR Part 312), New Drug Applications (21 CFR Part 314) , Drug Master Files (21 CFR Part 314.420) , and Biologics License Applications (21 CFR Part 601) referred to in this application.
10. IND submission should be consecutively numbered. The initial IND should be numbered "Serial number: 0000." The next submission (e.g., amendment, report, or correspondence) should be numbered "Serial Number: 0001." Subsequent submissions should be numbered consecutively in the order in which they are submitted..
    Serial Number ____
11. This submission contains the following *(Select all that apply)*
    ☐ Initial Investigational New Drug Application (IND)
    ☐ Request For Reactivation Or Reinstatement
    ☐ Response to Clinical Hold
    ☐ Annual Report
    ☐ Response To FDA Request For Information
    ☐ General Correspondence

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SECTION 2: TABLE OF CONTENTS

INVESTIGATIONAL NEW DRUG APPLICATION

Use of DRUG to evaluate DISORDER in infants

Sponsor-Investigator: John Smith, MD
The Children's Hospital of Philadelphia

TABLE OF CONTENTS

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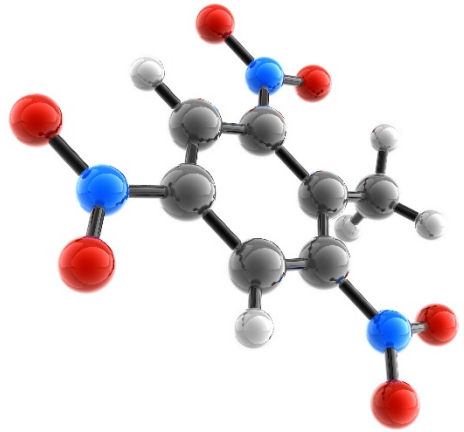
SECTION 3: INTRODUCTORY STATEMENT AND GENERAL INVESTIGATIONAL PLAN

- The brief introduction should include:
  - Name of the drug and all active ingredients
  - Drug's pharmacological class
  - Structural formula of the drug (if known)
  - Formulation of the dosage form(s) to be used
  - Route of administration
  - Broad objectives and planned duration of the proposed clinical investigation(s)



- The brief summary should include:
  - Previous human experience with the drug
  - Reference to other INDs if pertinent
  - Reference to investigational or marketing experience in other countries that may be relevant to the safety of the proposed study

SECTION 3: INTRODUCTORY STATEMENT AND GENERAL INVESTIGATIONAL PLAN

- Brief description of the plan for investigating the drug product for the following year including:
  - The rationale for the drug or the research study;
  - The indication(s) to be studied;
  - The general approach to evaluate the drug;
  - The estimated number of patients; and
  - Any potential severe risks

SECTION 4: PREVIOUS HUMAN EXPERIENCE WITH THE INVESTIGATIONAL DRUG

This section includes:

- Detailed information about other studies where this drug was investigated/used previously (including in other countries), as it is relevant to the:
  - safety of the use of the drug
  - the study rationale
  - the effectiveness of the study drug

- Publications used to support the IND should be included in the IND application

SECTION 5: INVESTIGATOR'S BROCHURE

- The Investigator's Brochure (IB) includes:
  - A brief description of the drug
  - A summary of the effects of the drug in the body
  - A description of possible risks and side effects to be anticipated
- Required for Multicenter Studies
- Over the course of the study, changes to the IB are required to be reported to the IRB and FDA
- If study drug is already FDA approved, include the Package Insert (not the IB)

SECTION 6: PROTOCOLS

Basic elements of a clinical protocol

1. Background/Significance/Rationale of Investigation
2. Investigational Product Information/Dose Rationale
3. Patient Population/Indication
4. Eligibility Criteria
5. Trial Endpoints/Schedule of Evaluations
6. Clinical Care vs Research Procedures
7. Safety Considerations/Risks/Stopping Rules
8. Data Safety Monitoring Plan/Safety Reporting/Management
9. Investigational Product Handling/Accountability
10. Regulatory Considerations: FDA and IRB Requirements
11. Publication Considerations
12. References

ONE PROTOCOL FOR EACH PLANNED STUDY

- The clinical protocol on file with the IRB, FDA and DSMB (if applicable) should be the **same (identical) version**
- Any change to the clinical protocol should be updated with the IRB, FDA and DSMB (if applicable), to ensure that each regulatory group has the identical protocol version
  - Include a **new version date** every time the protocol is updated

SECTION 7: CHEMISTRY, MANUFACTURING, AND CONTROLS (CMC)

- Describes the composition, manufacture, and control of the study drug.
- When the manufacturing of the investigational product occurs at CHOP or at Penn, the CMC section will be written by the manufacturer of the investigational product at CHOP or Penn.
- For most IND studies at CHOP, the CMC section is replaced by the Package Insert
- Good manufacturing practice (GMP) guidelines provide guidance for manufacturing, testing, and quality assurance in order to ensure that a drug product is safe for human consumption.

Please see supplement for additional information about CMCs and GMP

GOOD MANUFACTURING PRACTICES (GMP)

- GMP guidelines are a series of general principles and practices that must be observed during manufacturing.
- GMP guidelines provide guidance for manufacturing, testing, and quality assurance with the goal of safeguarding the health of patients as well as producing good quality medicine, medical devices, or active pharmaceutical products.
- Following GMP is mandatory in pharmaceutical manufacturing.

SECTION 8: PHARMACOLOGY AND TOXICOLOGY

- Information in this section comes from pre-clinical data collected from animal testing or in vitro.
- Describes how the study drug works in the body (absorption, distribution, metabolism and excretion)
- Summarizes the effects of the drug in the body (usually tabulated)

SECTION 9: ADDITIONAL INFORMATION

In certain applications, information on special topics may be needed.

- Drugs with a dependence and/or abuse potential:
  - information from other studies of that drug
  - what additional protections are in place to mitigate these potential issues
- Radioactive drugs:
  - a calculation of how much radiation is absorbed and potential impact on the body/organs.
  - phase 1 studies of radioactive drugs must include background information on how to calculate the dose of radiation absorbed in the body.

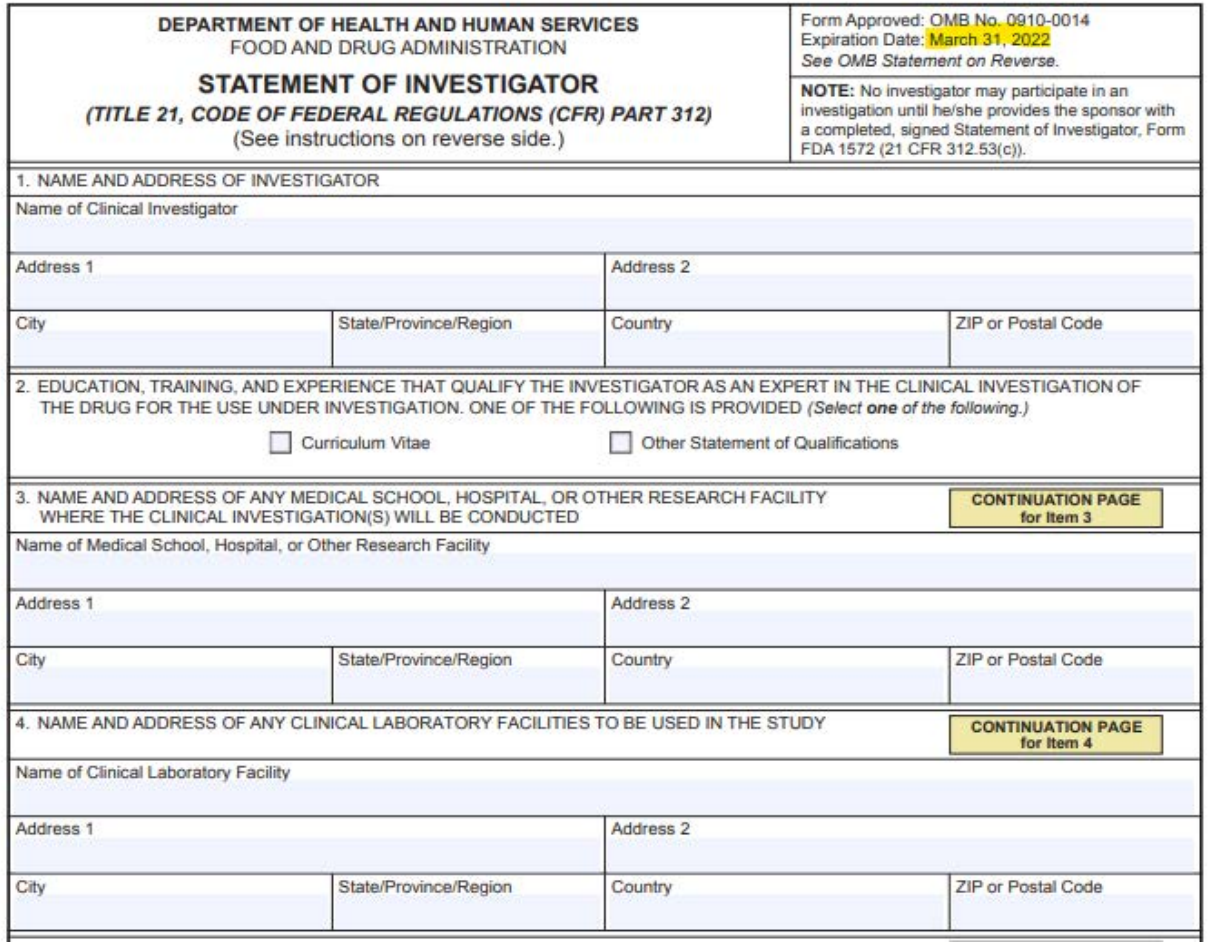
STATEMENT OF INVESTIGATOR: FDA FORM 1572

This form serves two purposes:

1) Provides site and investigator information

2) The Investigator agrees to conduct research according to FDA regulations

- This form is required for each site that is participating in the study



DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

STATEMENT OF INVESTIGATOR
(TITLE 21, CODE OF FEDERAL REGULATIONS (CFR) PART 312)
(See instructions on reverse side.)

Form Approved: OMB No. 0910-0014
Expiration Date: March 31, 2022
See OMB Statement on Reverse.

NOTE: No investigator may participate in an investigation until he/she provides the sponsor with a completed, signed Statement of Investigator, Form FDA 1572 (21 CFR 312.53(c)).

1. NAME AND ADDRESS OF INVESTIGATOR

Name of Clinical Investigator

Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

2. EDUCATION, TRAINING, AND EXPERIENCE THAT QUALIFY THE INVESTIGATOR AS AN EXPERT IN THE CLINICAL INVESTIGATION OF THE DRUG FOR THE USE UNDER INVESTIGATION. ONE OF THE FOLLOWING IS PROVIDED *(Select **one** of the following.)*

☐ Curriculum Vitae ☐ Other Statement of Qualifications

3. NAME AND ADDRESS OF ANY MEDICAL SCHOOL, HOSPITAL, OR OTHER RESEARCH FACILITY WHERE THE CLINICAL INVESTIGATION(S) WILL BE CONDUCTED — CONTINUATION PAGE for Item 3

Name of Medical School, Hospital, or Other Research Facility

Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

4. NAME AND ADDRESS OF ANY CLINICAL LABORATORY FACILITIES TO BE USED IN THE STUDY — CONTINUATION PAGE for Item 4

Name of Clinical Laboratory Facility

Address 1		Address 2	
City	State/Province/Region	Country	ZIP or Postal Code

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FDA FORM 3674
CLINICALTRIALS.GOV REGISTRATION

- Purpose: Form 3674 is a signed statement that the Sponsor will comply with clinicaltrials.gov requirements.
- To establish a clinicaltrials.gov account please contact:

  Office of Research Compliance
  ORC@email.chop.edu

FDA FORM 3926
SINGLE SUBJECT IND

- FDA Form 3926 is a streamlined IND application for a single subject (for either non-emergency sINDs or emergency sINDs)
  - Elements
    - Subject description and clinical course
    - Investigational drug description and rationale for use in the subject
    - Treatment plan
    - Dose modification plan - For example, if ineffective at a given dose or toxicity at a certain dose
    - Adverse event reporting – Identification of toxicity scale, or definitions of severity grades
    - Adverse event reporting to include IRB, FDA, drug manufacturer and DSMB (if applicable)
    - Monitoring plan

IND DETERMINATIONS: WHAT TO EXPECT FROM THE FDA

FDA SUBMISSION PROCESS

- IND is entered into the FDA tracking system DARRTS (Document Archiving, Reporting, and Regulatory Tracking System)
- IND is assigned to a division, and to a Regulatory Project Manager (RPM) within that division.
- The RPM will send an IND acknowledgement letter.
- Reviewers from three divisions are assigned to the study.
- Within those first 30 days, Sponsor should be available to answer any questions from the FDA

FDA RESPONSES

RESPONSES FOR EXPANDED ACCESS INDS

- **Non Emergency Single Subject or Treatment IND**
  - Single Subject INDs may be permitted to proceed prior to the 30 day review period, but ONLY if written approval is granted by the FDA.
- **Emergency IND**
  - The FDA will respond via phone, email, or with a formal letter within 24 hours with approval or disapproval of the application request.

RESPONSES FOR CLINICAL INVESTIGATION INDS

- RPM will communicate any questions that reviewers have within that first 30 days. Answers to these questions may result in changes to the protocol or other supporting documents.
- The Sponsor may not receive a formal “OK to Proceed” letter from the FDA, but can begin the study 30 days from FDA receipt of submission.
- If the questions are not answered to the satisfaction of the FDA, the study will be placed on “clinical hold,” which is not punitive.
- As soon as possible, but no later than 30 days, a "CLINICAL HOLD" letter will be sent to the Sponsor
  - Full Clinical Hold: study may not proceed until the questions are answered and FDA formally allows the study to proceed.
  - Partial Clinical Hold: delay or suspension of only part of the study

21 CFR 312.42

SPECIFIC EXAMPLES OF CLINICAL HOLDS

- Manufacturing Information/Drug Quality
  - ✓Impurity profile presents health hazard
  - ✓Chemical stability is inadequate
- Pharmacology and Toxicology
  - ✓Studies are not sufficient
  - ✓Studies are poor quality (non GLP)
- Clinical Protocol
  - ✓Prior toxicities are not addressed
  - ✓High potential for unpredictable acute reaction without consideration of staggered administration

KEY POINTS TO REMEMBER:

- Material in a foreign language:
  - If any material in the IND application is not in English, provide the original document and an English translation.
- Number of copies:
  - All submissions sent to the FDA should consist of an original and two copies.
- Numbering of IND submissions:
  - The initial IND is numbered 0000; each subsequent submission (e.g., amendment, report, correspondence) is numbered serially (0001, 0002, 0003, etc).
- Per CHOP Policy, all FDA Correspondence is required to be provided to IND/IDE Support (INDIDE@email.chop.edu).

REFERENCES

- 21 CFR 312
- FDA Presentations (2009 and 2011)
- CFR - Code of Federal Regulations: 21 CFR 312
  - Title 21 Food and Drugs
  - Chapter 1 FDA DHHS Subchapter D
  - Subchapter D Drugs for Human Use
  - Part 312 Investigational New Drug Application

SBA Educational Forum
October 15, 2009

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