Questions Every Investigator Should Ask BEFORE Doing Research with a Drug, Device or Biologic

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Translational Research Program
www.childrenshospital.org/trp

Definitions

- FDA – Food and Drug Administration
- IND – Investigational New Drug Application
- IDE – Investigational Device Exception
- CDER – Center for Drug Evaluation and Research
- CBER – Center for Biologics Evaluation and Research
- CDRH – Center for Device and Radiological Health

Section Objectives

- Describe investigator and sponsor responsibilities
- Review regulatory requirements for research involving drugs, devices and biologics
- Define what types of products are considered drugs, devices or biologics
- Determine required Regulatory Reviews
- Provide details of investigator support resources available at Children’s

What is a regulation?

- They are not laws – Laws are statues which must be followed according to how they are written
- Regulations are guidelines that must be followed but are open to interpretation
- The regulations are vague in areas to allow science to grow but also to allow the FDA the ability to regulate as science grow
- The FDA review team’s interpretation is the one that only counts
What is a regulation?

- Just like different IRB's, Grant or Journals reviewers, how regulations are interpreted can be different depending on who is doing the interpreting.
- To ensure the smoothest review process you should do everything in your power to follow the regulations to the best of your ability.
- When in doubt contact FDA, get response in writing.
- For assistance contact Matt Wladkowski – matthew.wladkowski@childrens.harvard.edu ; X42777

Who are the players in a clinical or translational investigation?

Who are the players?

- **Sponsor** – A person who takes responsibility for and initiates a clinical investigation (Signature on "the 1571")
- **Investigator** – An individual who actually conducts a clinical investigation (Signature on "the 1572")
  - The investigator is responsible for how the test article is administered and/or dispensed.
- **Sponsor-Investigator** – An individual who both initiates and conducts an investigation, and under whose immediate direction the test article is administered.

  **Please Note:** The sponsor (sponsor –investigator) is responsible for your project's regulatory obligations, **NOT Children's**!

What are the Sponsor’s Responsibilities?

- Selecting qualified investigators and monitors
- Informing investigators
- Monitoring ongoing investigation
- Record keeping and retention
- Ensuring the return or proper disposal of unused investigational drug supplies

  **Please Note:** A Sponsor-Investigator is responsible for all of above.
What are the Investigator’s Responsibilities?

- Compliance with the Investigator’s Statement (Form FDA-1572)
- Assurance of IRB review
- Control of the investigational product
- Record keeping and Record retention
- Investigator reports
- Please Note: A Sponsor-Investigator is responsible for all of above

You have an idea for a new study with a drug, device or biologic... now what?

Questions to ask yourself

- What is the difference between off-label use and research?
- Am I using an “investigational product”?
- What sort of reviews and approvals do I need to begin my project?
- Do I need an IND or IDE to conduct my study?
- What should the “regulatory strategy” be for my product/study?
- What resources are available at Children’s to help me with my responsibilities as an Sponsor and/or Investigator?

What is the difference between Off-Label Use and Research?

- **Off-Label Use** – Physician prescribes approved medications for uses beyond their label
  - The physician’s motivation must solely benefit the well-being of an individual patient

- **Research use** – regulated to ensure well designed protocols, evaluate drug safety and efficacy and the protection of human subjects
  - Research is designed to test an hypothesis, draw conclusions and contribute to knowledge, theories and principals
What is an Investigational Product?

• An *unapproved* pharmaceutical form of an active ingredient or placebo that is being tested OR an *unapproved device* used as a reference in a clinical trial. Includes,
  – already approved products that are being used or assembled in a way different from the approved form
  – approved products that are being used for an unauthorized indication or to gain further information

Is your investigational product considered a drug, device or biologic?

What is a drug?

• **Drug** - Anything that achieves its primary intended purpose through chemical action within or on the body and is dependent upon being metabolized to achieve its purpose.
  – Examples: Over the counter drugs, prescription drugs, new substances, biologics and combination devices

• If the substance used in your study is unapproved for the indication and its purpose is to *treat, cure, diagnose, or prevent a disease or condition*, in all likelihood it will be considered an Investigational drug and an IND will be required.

What are Biologics and Devices?

• **Biologic** - Product that replicates natural substances such as enzymes, antibodies, or hormones
  – Biologics go through the same approval process (IND) as drugs, but are reviewed by CBER

• **Device** - Instrument/software/etc. that achieves its intended purpose through physical action rather than chemical action or metabolism
  – Devices are reviewed through the Investigational Device Exemption process done by CDRH
Significant Risk Device vs. Non-Significant Risk Device

- An IDE is required if a device is determined to be of Significant Risk (SR)
- The process to determine a device’s risk level:
  - Sponsor provides a description of the device, and why the device qualifies as an SR or NSR device
  - Investigator submits description with application to the IRB
  - The IRB reviews and makes a final determination, unless the FDA has made a determination prior

Criteria for a Significant Risk Device

- Intended as an implant
  - Duration of implantation should be specified
- Used to support or sustain human life
- Considered of substantial importance in diagnosing, curing, mitigating, or treating disease
- Otherwise increases the potential for serious risks to the health, safety, or welfare of a subject
- Please Note: If your device is a NSR device you still have additional responsibilities

Case Scenario – “Active Bottle”

- The “Active Bottle” is a computer-controlled milk delivery system designed to help preterm infants to develop coordination skills of sucking, swallowing and breathing.
- Goal: whether the use the “Active Bottle” reduces the oral feeding difficulties experienced by preterm infants
- A nurse will feed the infant, but a computer will control the milk flow from the bottle nipple to the baby’s mouth.
- The computer program will look at the infant’s breathing in order to determine how much milk to provide from the bottle when the baby starts sucking.
- The device is designed so milk cannot flow from the nipple to the infant’s mouth unless the infant breathes properly.

Quiz - Is this Device a SR device?

- Is this device intended as an implant
  - No
- Will it be used to support or sustain human life
  - No, the infants can still be fed without device
- Does this device constitute substantial importance in diagnosing, curing, mitigating, or treating disease
  - No, its purpose is to help preterm infants to develop coordination skills of sucking, swallowing and breathing
- Does this device otherwise present a potential for serious risk to the health, safety, or welfare of a subject
  - No
**INDs vs. IDEs**

- Both applications require Investigator Qualifications, Investigational Plan and Protocol, Labeling/Indication information
- IDEs focus on engineering, materials and how a device functions
- INDs focus on chemistry, manufacturing and how a drug interacts in the body
- In general, much easier/faster to get a device approved

**What is the purpose of an IND?**

- An Investigational New Drug (IND) application fulfills two regulatory requirements
  - Notifying the FDA of intent to study test article
  - Allowing interstate transport of the test article
- An IND also provides an additional level of protection
- Affirms the body of knowledge about the manufacturing, pharmacology, and toxicology of the drug
- Ensures investigation is conducted in accordance with Good Clinical Practices (GCPs)

**When is an IND not required?**

- Drug is legally marketed for indicated use
  - No new indication or significant labeling change
  - No significant change in advertising
  - No change in route of administration, dosage, patient population
  - No use that significantly increases patient risks
- Includes drugs intended for testing in vitro or in animals
  - Placebo Products
  - Generic Drug Production
**What about Medical Foods and Supplements?**

- **Medical Food** – Prescribed by a physician when a patient has a special nutrient need in order to manage a disease or health condition. Part of a physician’s ongoing care.
- **Supplement** – Same as medical foods except NOT PRESCRIBED by a physician.
- There are currently no safety evaluations, standards for claims or specific information required on labels for either product.
- Please note: If either product is used in a study to treat, cure, diagnose, or prevent disease, it is considered a drug.

**Case Scenario**

- **Case Scenario:** Omega-3 fatty acid (fish oil) for treating medicated adolescents with major depression (1 capsule 2x a day).
- Omega-3 fatty acid has been shown to play a role in affecting brain chemical responsible regulating mood and reducing depression in medicated patients.
- Imaging and blood tests will be conducted to examine potential indicators of treatment response to omega fatty acids in adolescents with a high risk for depression.

**Quiz Time**

- Is this a drug?
- **YES!** – Omega-3 is a substance that achieves its intended purpose by being metabolized. The substance is being used to treat a condition, clinical depression.
- Does this study need an IND?
- **YES!** - This study is designed to support a new indication for Omega-3, depression.
- If the study was designed to show that Omega-3 would lower, improve, reduce, etc. the patients condition a IND may not be needed...the key word is TREAT.

**Beyond the FDA...**

- Other potential required regulatory approvals for protocols involving drugs, devices or biologics:
  1. Internal Scientific Review
     - All protocols are required to undergo Department/Division scientific review prior to CCI submission.
  2. Bio-safety Review (COMS)
     - RDNA, Virus, Gene transfer, Bacteria, etc.
  3. Recombinant DNA Committee (RAC) Review
     - NIH Committee
  4. Study Specific approvals – Lab, personnel, etc.
**Regulatory Strategy**

- Investigators need to understand both the regulatory landscape and relevant precedents
- Understanding of both areas will build the framework for the overall plan and determine the fastest or most effective path to approval
- Your regulatory strategy should be a living document that is regularly revised based on scientific results, as well as changes in the regulatory environment

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**IND application**

The application must contain information about three broad areas:

1. The results and analysis of all pre-clinical testing (Animal/Toxicology Studies)
2. Analysis of the drug’s composition, as well as manufacturing and quality control procedures during production of compound
   - Letter of authorization from Drug Company
3. Sponsor’s plans for initial proposed clinical studies and qualifications of the investigators

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**“Ideal” Regulatory Review Flow**

- If your study uses rDNA or Virus:
  - COMS (Harvard) → RAC Review (NIH)
  - FDA
  - IND → IDE

- Children’s Review
  - Departmental Review → CCI (IRB) Review
Pre-Clinical Testing

• Basic/animal testing is vital to FDA determination of whether a test article/treatment is safe and effective in humans
• If you do not have experience in basic/clinical testing, there is a good chance someone at Children’s has experience in your therapeutic area…make friends!
  — Of great benefit to both the scientist and clinician
  — Helps take both their work to the next level
• Seek out Translational Research Program at CHB
  — Mission to help connect people at CHB to promote translational research

Pre-Clinical Testing

• Questions that should be answered:
  — Can the drug be validated?
  — How safe is the drug? Is it effective?
  — How much can you put into an animal before it dies?
  — Why should the FDA believe that this animal model is comparable to a human?
• Pre-IND meeting with the FDA – A Sponsor requested formal meeting to discuss testing and data requirements and any other scientific issues w/ the FDA that may need to be resolved before IND submission (Contact Matt Wladkowski for assistance)
• Meeting is not required but recommended when Investigators are unsure of the testing requirements

IND/IDE Registry

• Web-based listing of open Sponsor-Investigator INDs/IDEs at Children’s Hospital
• Registry keeps track of important regulatory info about your projects
• Registered studies will receive additional services from the IND/IDE Service
  — Reminders to you when annual reviews are due
  — Guidance and assistance in preparation of documents
• Provides the Institution with a record of INDs/IDEs in case of audit
• Contact Matt Wladkowski for more info – matthew.wladkowski@childrens.harvard.edu; X42777
When can I start my study under my IND?

- FDA is required to respond to an IND sponsor within 30 calendar days of receipt
- FDA may grant approval OR an exemption OR place a Complete or Partial Clinical Hold with the intention of delaying the proposed clinical investigation
- You may begin your study after the 30 calendar days UNLESS you are contacted
- No News = Good News!

Things to keep in mind...

- Each step of the process helps put the larger puzzle together
- Each step is not singular event
- Keeping your study in compliance is a continuous process which starts at when you conceive your idea and ends when you officially close your study with the FDA
- Each study is unique. Just because you did/didn’t do something on a previous study does not mean the same process can be applied to your next study

So where do I begin?

- Document Check List
  - Protocol and Informed Consent
  - Investigational Brochure
  - Letter of Authorization
  - Pre-Clinical and/or Human Testing results
  - Any journal articles that supports your study is safe and effective in Humans
- Contact Matt Wladkowski – matt.wladkowski@childrens.harvard.edu; X42777

Regulatory Resources Page

- Please visit the Regulatory Resources page on the Translational Research Program Website
  - www.childrenshospital.org/trp
- Will find basic Regulatory Information, FDA Forms and Guidance, Reporting Requirements and the CHB IND/IDE Registry
- If you have any regulatory questions, please feel free to contact Matt Wladkowski – matthew.wladkowski@childrens.harvard.edu; X42777
Who at Children’s can help me with my responsibilities???

Adam C Simmons, MPH, CCRC
Senior Clinical Research Specialist
Clinical Research Program

So Matt just told me about what I need to do for a regulated trial...

The clinical & translational research roadmap...

Factors that will affect your personal roadmap

- Your research question
- The “Product” you study
- Regulations
- No two maps are the same
Objectives

- Not have your path look like this...

Clinical Research Program (CRP)
http://web2.tch.harvard.edu/crp

What can CRP do for me?
What can CRP do for me?

- Clinical trial design
- Case Report Form development
- Survey Design
- Data and Safety Monitoring Plans
- Data management
- Randomization
- Data Analysis
- Education

Regulations highly affect these aspects

Clinical Trial Design

- CRP will help you define your objective
- Power analysis and sample size
- Designed to fulfill your required regulatory requirements
- Controls to prevent bias (randomization, inclusion/exclusion criteria)
- Feasible (recruitment, time, $$$)
Data and Safety Monitoring Plans

These procedures vary by study...CRP can help you develop them!!!

Data Management

- Documentation (if it isn’t written down...)
- FDA will compare your final data (as a CRF, EDC) to the source where it was first recorded
- To an FDA auditor your study should “read like a book”...including the chapters you’ve changed!

Your responsibility

Your CRP Tool

→ Assistance with CRF development

→ Electronic Data Capture (EDC) databases (CRP recommends for FDA regulated studies)

→ Assistance with developing study manuals of operations for data management procedures

What can CRP do for me?

- Clinical trial design
- Case Report Form development
- Survey Design
- Data and Safety Monitoring Plans
- Data management
- Randomization
- Data Analysis
- Education

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Objectives

TIDO

CBO

CTO

TRP

Research Nursing

EQuIP

CRP

WHO at Children’s Can Help?

Sponsor/Investigators’ Responsibilities...
Research Pharmacy
Rocco “Rocky” Anzaldi, RPh; Rocco.Anzaldi@childrens.harvard.edu

Research Pharmacy
• Feasibility
• Manufacturing
• Issues that are overlooked
  – Availability of pediatric preparation
  – Shelf life of drug vs. duration of trial
  – If a matching placebo can be prepared
  – Special instructions for parents
  – Budgeting

BEFORE you submit your IND consider…

Research Pharmacy
• As the IND holder of a Drug trial YOU not the pharmacy are ultimately accountable for your drug
• Have well developed pharmacy procedures
• Meet with Rocky early!

Drug Accountability!

Objectives
TIDO
CTO
CBO
Research Nursing
TRP

Sponsor/Investigators’ Responsibilities…

WHO at Children’s Can Help?

Research Pharmacy

EQuIP
CC
CRP
Office of Clinical Investigation (IRB)
• CCI review is STILL required for ALL protocols involving human subject
• CITI Training STILL required for all researchers involved with human subjects
• This is in addition to FDA review if required

Office of Clinical Investigation (IRB)
• The CCI will not approve a FDA regulated study until FDA approval, but you may submit your study prior to FDA approval
• Your study must receive BOTH FDA and CCI approve before any subjects can be enrolled into your study
• A CCI contact list is available in the back
Technology and Innovation Development Office (TIDO)

- The translation from bench to bedside becomes very public!
- Patents and potential patents
- Publishing rights

Technology and Innovation Development Office (TIDO)

Industry Partners

Budgets

Intellectual Property

Multi-center Collaboration

- Clinical Trials Office (CTO)
  - Point of contact for negotiations with industry (MTAs, CTAs...)
  - If you sponsor a multi-center trial you will need a clinical trial agreement with them
Technology and Innovation Development Office (TIDO)

Central Budget Office (CBO)
- Will help investigators build a budget for clinical services done for research purposes
- Will create tracking sheets to bill to your fund number
- IRB will not release a protocol without CBO sign off!

TIDO Contacts in the back of the room!

EQuIP
Education and Quality Improvement Program
www.childrenshospital.org/research/equip

EQuIP Services
- Study reviews
- Study pre-review and set-up
- New Investigator Pre-Reviews
- IND/IDE Holders Pre-Review
- Study Monitoring
- Education
**EQuIP Services**

- Study reviews
- Study pre-review and set-up
- New Investigator Pre-Reviews
- IND/IDE Holders Pre-Review
- Study Monitoring
- Education

*Required for FDA regulated studies*

**IND/IDE Holders Pre-Review**

- If you hold an IND/IDE EQuIP will meet with you to overview your FDA responsibilities
- This is meeting is required before CCI will approve your protocol

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**EQuIP Services**

- Study reviews
- Study pre-review and set-up
- New Investigator Pre-Reviews
- IND/IDE Holders Pre-Review
- Study Monitoring
- Education

*Required for FDA regulated studies*

**Study Monitoring**

- FDA regulations require sponsors of clinical investigations monitor the progress of a clinical investigation to ensure:
  - Adequate protection of the rights of human subjects
  - The safety of all subjects involved in clinical investigations and,
  - The quality and integrity of the resulting data submitted to the FDA.
How a Research Nurse can help with your FDA regulated trial

- As an FDA investigator you agreed to;

  “ensure that all associates, colleagues, and employees assisting in the conduct of the study(ies) are informed about their obligations in meeting [the above] commitments.”

-FDA Form 1572 Section 9: Commitments of the Investigator

How a Research Nurse can help with your FDA regulated trial

- Can manage and administer the Investigational product
- Monitor subjects receiving investigational product
- Facilitate the training of bedside nursing staff on the protocol and their delegated study responsibilities
Off-Unit Research Nurses

When to contact:

• When you start developing your clinical operations
• Any ongoing studies you have where the clinical nursing staff doesn’t know about their research responsibilities!

Translational Research Program (TRP)
www.childrenshospital.org/trp

The mission of the TRP is to stimulate the development of non-clinical and human clinical trials that seek to improve the care of children, and to ensure adequate infrastructure to support non-clinical and clinical translational research projects.

IND/IDE Service

• Please visit the Regulatory Resource page on the TRP website: www.childrenshospital.org/trp
• The website provides basic regulatory information, Submission format, FDA forms and guidance, and the CHB IND/IDE registry
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Grant and Retreats Opportunities

- Grant opportunities are available for projects that relate to the goals of the TRP
  - Emphasis on projects containing novel ideas for which there is a reasonable expectation of human trials
- The deadline for the next funding cycle is February 2010
- Support also available for multidisciplinary Retreats/Workshops/Symposia on or off campus
- Please visit the TRP website for details: www.childrenshospital.org/trp

Want more???

We would love your feedback...

Don’t forget to see program representatives in the back!!!