The Children’s Hospital of Philadelphia®
RESEARCH INSTITUTE
The Scope of Human Subjects Research at The Children’s Hospital of Philadelphia

Case Studies in Translational Research
Perelman School of Medicine
University of Pennsylvania
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Office of Clinical and Translational Research
The Children’s Hospital of Philadelphia
Outline

• Scope of Human Subjects Research at CHOP

• Brief History of Modern Pediatric Research that Transformed the Pediatric Regulations

• Case Studies
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• Case Studies
What is Research

- HHS Regulations define research as “a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge”

- FDA focuses on whether or not an investigational test article is used – even if the article is used in only one person (“Clinical Investigation”)
Non-Research

• Examples of non-research
  · Case Report or Case Series
  · Quality Improvement

• Under some circumstances, both types of activity may qualify as research
Is it Human Subjects Research?

- Human subject is a living individual about whom an investigator conducting research obtains:
  - Data through intervention, or
  - Interaction with the individual, or with
  - Identifiable private information
    - Must be individually identifiable
    - Different standard than HIPAA
Institutional Review Board (IRB) Definition

“...any board, committee, or other group formally designated by an institution to review, to approve the initiation of, and to conduct periodic review of, biomedical research involving human subjects. The primary purpose of such review is to assure the protection of the rights and welfare of the human subjects.”

FDA 21 CFR §56.101-124
Protocol Submitted

Is this research?

Human Subjects?

IRB Must Review

No

STOP

Yes

Yes

STOP

No
IRB Review

Is it Exempt?

Yes: Issue Letter Confirming Exemption

No: Expedited Review?

Yes: Review by IRB Chair

No: Review by full Board
Exempt Research

• Exempt research does not require IRB oversight but at CHOP the IRB must make the determination that research is exempt.

• Research must be minimal risk and fit into one of six regulatory categories (for example: surveys, retrospective research without identifiers, educational research).
Expedited Review

- Expedited review is a procedure during which review may be carried out by the IRB chairperson or by one or more experienced reviewers designated by the IRB chairperson from among the members of the IRB.

- In reviewing the research, the reviewers may exercise all of the authorities of the IRB except that the reviewers may not disapprove the research.
Full Board Review

- IRB has the authority to:
  - Approve
  - Require modifications (to secure approval)
  - Disapprove any research activities

- If the IRB does not have sufficient information to make a determination, the IRB will defer the vote

- If the research is disapproved, the IRB will provide the reasons for its decision and give the opportunity to respond
Criteria for Approval

• In order to approve a research protocol the IRB must determine that the protocol meets the regulatory criteria for approval.

• These criteria include:
  • Risks to subjects are reasonable and minimized
  • Selection of subjects is equitable
  • Informed consent is sought
  • Protections for vulnerable populations (e.g. children)
Scope of Human Research Studies: Examples

- Review of public records
- Review of patient health records
- Studies based on questionnaires
- Studies of behavior, some with ‘health-related behavioral or biomedical outcomes’, that is, a clinical trial
- Studies involving collection of health information, or of biological samples, or of imaging results
- Clinical trials (drugs, devices, biologics, behavioral) without FDA oversight
- Clinical trials with FDA oversight: Randomized, prospective, blinded, placebo-controlled, multi-site; cross-over
- Clinical Trials with Adaptive Design
- Comparative effectiveness trials (chart review, versus interventional)
- N-of-1 trials
Overview of Human Subjects Research at CHOP

- Total number of human subjects trials
- Total number of non-clinical trials
- Total number of clinical research trials:
  - Phase 1-4 distribution
  - Government vs Non-Government Funding
  - FDA-Regulated Drug and Device Sponsor-Investigators at CHOP ("Hold the IND or IDE", and assume regulatory responsibility for the clinical research study)
## Research at CHOP: Metrics

<table>
<thead>
<tr>
<th>Type of Research</th>
<th>Number of Studies/ Percentage of Research*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not Human Subjects Research: Includes QI and research without interaction of living humans or their PHI</td>
<td>Uncertain # of NHSR</td>
</tr>
<tr>
<td>Human Subjects Research Total</td>
<td>2113</td>
</tr>
<tr>
<td>Clinical Trial HSR</td>
<td>540 (26%)</td>
</tr>
<tr>
<td>Non-Clinical Trial HSR</td>
<td>1573 (74%)</td>
</tr>
<tr>
<td><strong>Total Research Projects</strong></td>
<td><strong>2113 (100%) + NHSR</strong></td>
</tr>
</tbody>
</table>

* Q1, 2016
Funding Sources for Human Subjects Research: Examples

• Federal: NIH, DoD, FDA (Orphan Products)
• State: Tax Sources; State Propositions; Legal Settlements
• Industry: Pharmaceutical companies, biotechs
• Institutional: Divisional, Departmental
• Academia: Penn ITMAT
• Philanthropic: Howard Hughes, Doris Duke
• Patient Advocate Groups
• Benefactors
• Academic-Industry Collaborations
NIH Definition of Clinical Trial

A research study in which one or more human subjects are prospectively assigned to one or more interventions (which may include placebo or other control) to evaluate the effects of those interventions on health-related biomedical or behavioral outcomes.
# Standard of Care vs Clinical Trial: Different Obligations

## Standard of Care
- First, do no harm
- Provide best medical practices

## Clinical Trial
- Develop Protocol with Sound Design
- Minimize Risks
- Optimize Risk/Benefit Ratio
- Protect Rights, Safety, Well-being of Subjects
- Compliant Study Conduct
- Complete & Accurate Documentation/Data Integrity
- Report Knowledge Gained
- Potential Product Development
Does the study involve one or more human subjects?

No

Does the study involve the use of one or more interventions?

No

The study is not a clinical trial.

Yes

Does the study prospectively assign human subject(s) to an intervention(s)?

No

Yes

Does the study have a health-related biomedical or behavioral outcome(s)?

No

Yes

The study is a clinical trial.
Examples of Clinical Trials

• Prospective interventional study of drug, biologic or device
• Prospective behavioral study measuring a health-related outcome
• Prospective surgical intervention assessing a health-related outcome
Clinical Research at CHOP: Phases

<table>
<thead>
<tr>
<th>Phase of Clinical Trial</th>
<th>% of Approved, Open Trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pilot/Phase 1</td>
<td>27%</td>
</tr>
<tr>
<td>Phase 1</td>
<td>11%</td>
</tr>
<tr>
<td>Phase 2</td>
<td>28%</td>
</tr>
<tr>
<td>Phase 3</td>
<td>28%</td>
</tr>
<tr>
<td>Phase 4</td>
<td>6%</td>
</tr>
<tr>
<td>Total Clinical Trials</td>
<td>100%</td>
</tr>
</tbody>
</table>

* As of Q1, 2016
<table>
<thead>
<tr>
<th>Funding Source</th>
<th>% of Approved, Open Trials*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Federal Government (NIH, DoD)</td>
<td>35%</td>
</tr>
<tr>
<td>Industry (Pharma, Biotech)</td>
<td>30%</td>
</tr>
<tr>
<td>Institutional, Philanthropy, Local &amp; State Funding, Other</td>
<td>35%</td>
</tr>
<tr>
<td><strong>Total Clinical Trials</strong></td>
<td><strong>100%</strong></td>
</tr>
</tbody>
</table>

* As of Q1, 2016
Sponsor-Investigator Initiated
FDA-Regulated Clinical Trials at CHOP

~40 of >540 currently open clinical trials are sponsor-investigator initiated, that is, the S-I ‘holds’ the IND or IDE.
FDA-Regulated Clinical Trials

Product Applications
• Investigational New Drug (IND)
• Investigational Device Exemption (IDE)

For
• Drugs (CDER),
• Biologics (CBER),
• Devices (CDRH),

...that are used in a clinical study with intent to cure, mitigate, prevent, treat or diagnose a condition or disease (or change the structure or function of the body)
IND Applications: Key Elements

IND Application Key Components

Clinical Protocols and Investigator Information
1. Form FDA 1572
2. CV of Sponsor-Investigator
3. Clinical Protocol – how to monitor safety
4. Clinical SOPs

Pharmacology and Toxicology
1. Preclinical Data
2. Pharmacokinetics
3. Investigator Brochure
4. Prior Human Experience (if applicable)

Manufacturing Information
1. All Drug Components and Placebo
2. Chemistry, Manufacturing and Controls
3. Labeling Information
4. Laboratory SOPs
Does FDA Oversee Every Clinical Trial?

- Some trials do not fall under FDA regulations:
  - IND exempt trials are approvable by the IRB
  - Trials involving only NSR devices are approvable by the IRB
  - Behavioral trials with health-related outcome
  - Surgical trials
  - Some comparative effectiveness trials
Keys to FDA IND Exemption

• IND-Exempt Trials
  - Clinical trials that do not aim to diagnose, mitigate, cure, treat or prevent disease
  - Key requirements to meet IND exemption criteria
    - FDA approved, marketed drug
    - Labeling, marketing plans
    - Dose, formulation, route of administration
    - Risk analysis in newly proposed population
Drug Development Overview

- Basic Science
- Translational
- Pre IND
- Clinical
- NDA/BLA Review
- Post Marketing

Source FDA Pediatric Conference 9/2014
FDA Terms

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Milestones in the Regulation of Pediatric Drugs

- 1902 Biologics Control Act
- 1938 Food, Drug, and Cosmetic Act
- 1952-1962 Polio
- 1962 Kefauver-Harris Amendment
- 1983 Orphan Drugs Act
- 1994 Pediatric Labeling Rule
- 1997 Food and Drug Administration Modernization Act (FDAMA)
- 1998 Pediatric Rule
- 2002 Best Pharmaceuticals for Children Act (BPCA)
- 2003 Pediatric Research Equity Act (PREA)
- 2007 Re-Authorization of BPCA and PREA
- 2012 Congress codified BPCA and PREA into permanent laws, as the Food and Drug Administration Safety and Innovation Act (FDASIA)
Milestones in the Regulation of Pediatric Drugs

The St. Louis Tragedy, 1901

- Diphtheria patients routinely treated with antitoxin from equine serum
- Serum manufactured locally with no central or uniform controls
- In St. Louis in 1901, blood from a tetanus-infected retired milk wagon horse named Jim resulted in tragedy when 13 children given diphtheria antitoxin died of tetanus
- In 1902, Congress enacted the Biologics Control Act
Milestones in the Regulations of Pediatric Drugs

**Elixir Sulfanilamide**

- 1937: Sulfanilamide prepared with anti-freeze like solvent
- 206 people die, including a number of children
Polio

• Karl Landsteiner discovered polio virus in 1908
• Effect of polio epidemics in the 1950’s – Fear of polio was only second to that of the atomic bomb
• Basic research lab investigations increased
• Polio killed virus vaccine was initially discovered in 1952 by Jonas Salk’s group at the U of Pittsburgh
• Field test: 1.8 million children vaccinated, largest clinical test of a drug or vaccine in medical history
• Initial licensure of polio vaccine in 1955
Milestones in the Regulations of Pediatric Drugs

Cutter Incident

- Polio epidemics killed and disabled thousands in the early 1950s
- Polio-vaccinated children (and others exposed) developed abortive polio ($\approx 40,000$) and severe paralytic polio ($n \approx 170$) with 10 deaths in 1955
- Vaccination programs were suspended in the US
- Investigation revealed that Cutter Laboratories vaccine lots were contaminated with live polio virus
- More quality controls were implemented to ensure safety and efficacy
Milestones in the Regulations of Pediatric Drugs

Sabin Live Attenuated, Oral Polio Vaccine

- Sabin at the U Cincinnati hypothesized that live attenuated virus would provide longer-lasting immunity
- Tested in field trials in the Soviet Union between 1957-1959
- Licensed in the US in 1962
- Endorsed by AMA and was primary weapon for polio prevention by the end of the 1960s
Milestones in the Regulations of Pediatric Drugs

Thalidomide

1960s:
Approved in Europe for insomnia, morning sickness

Thousands of newborns affected
Milestones in the Regulations of Pediatric Drugs

Kefauver-Harris Amendment

- The 1962 Congressional response to the thalidomide crisis in Europe
- Francis Oldham Kelsey was the product reviewer who prevented the drug from study in the US
- Led to a change in the CFR, so that 45 CFR 46.405 was added to the pediatric regulations, ensuring that children’s study drugs, biologics and devices would be tested only if there is “a prospect of direct benefit.” Prior to this amendment, only the safety of drugs was considered.
Milestones in the Regulations of Pediatric Drugs

Implications of 45 CFR 46.405 on Pediatric Clinical Trials

• Since enactment, essential to demonstrate “prospect of direct benefit” for pediatric study participants in more than minimal risk trials

• First-in-human studies are conducted in adults, if there is an affected adult population, to demonstrate a prospect of direct benefit. In this context, children are enrolled only after a prospect of direct benefit is demonstrated first in the adult population

• If there are no adults with a disease or condition, the pre-clinical data in vitro and in animals in vivo are optimally sufficient to support a first study in children

• First-in-children studies are frequently stratified so that older pediatric subjects are enrolled prior to the youngest pediatric subjects
Milestones in the Regulations of Pediatric Drugs

Pediatric Rule, BPCA, PREA

- Pediatric Rule, 1998: FDA to oversee drug development for pediatric indications
- Best Pharmaceuticals for Children Act, 2002: “Carrot” providing for drug exclusivity
- Pediatric Research Equity Act, 2003: “Stick” mandating pediatric research studies
- Re-Authorization of BPCA & PREA, 2007
- Congressional action on BPCA & PREA, 2012: Codification to permanent law
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Case Study #1

You would like to collect data from autopsy reports as part of your research of the causes of death of children from 10-17 years of age in Philadelphia.

- Do you need IRB approval?
- Do you need approval from the institutional Office of Legal Counsel?
- Do you need FDA approval?
- Is a signed informed consent required for surviving families to permit review of the autopsy report?
- Does it matter in which state(s) you wish to conduct this study?
Case Study #2

You wish to use a drug approved and marketed in Canada, Mexico, the Caribbean and the EU to investigate its effect in the US on adults and children, for the indication on the label approved in all the jurisdictions described. The drug is not approved for marketing in the US.

- Do you need IRB approval?
- Do you need to file an FDA Investigational New Drug application?
- Does it matter that another institution in the US is already doing a study in adults and children for this same drug?
Case Study #3

You would like to use a drug approved and marketed for use in adults in the US, to investigate its effect on pediatric subjects for the same indication as that in adults. You cite the Pediatric Rule as your rationale for conducting the study.

• Do you need IRB approval?

• Do you need to file an Investigational New Drug application with FDA, or is the study exempt from FDA regulations?

• To claim exemption from IND filing, what is the crux of the case?

• Define “prospect” and “direct” in 45 CFR 46.405, “…prospect of direct benefit”
You want to use a drug for a cancer research study in children in the US. The drug is marketed for use in certain neoplasms in adults in the US, has no approval for cancer in children, yet a small proportion of children with a certain neoplasm, as well as the same underlying driver gene, should be targetable with the marketed drug.

A) What would be the simplest clinical study design to collect data of the usefulness of the drug for pediatric neoplasms?

B) Can you design a prospective study that would be IND exempt for this drug/indication?

What would the strengths and weaknesses of designs A & B?
You wish to use a biologic (viral gene therapy, in vivo) for congenital blindness in a US study. The disease has its onset in childhood, and the greatest benefit would be in the pediatric population. All pre-clinical data in tissue culture, mice, dogs and non-human primates show both safety and either efficacy (in affected mice and dogs) and the potential for efficacy in NHP (increased expression of transgene protein). Ongoing studies in both adults and children in the EU demonstrate safety of the approach, but insufficient long-term data is available to assess efficacy.

- Can the US study be initiated in children?
- What is the principle regulation underlying the IRB determination?
- How many adults does it take to demonstrate first-in-human efficacy, before proceeding to pediatric intervention trials?
You would like to use a biologic (normal donor hematopoietic stem cells) for Duchenne’s Muscular Dystrophy, injecting the normal HLA-matched donor stem cells into the coronary artery circulation of affected children to potentially improve their cardiac ejection fraction. From the same bank of normal hematopoietic stem cells injected into the coronary arteries of adult male patients with myocardial infarction (MI), scar formation S/P MI has reportedly been decreased one year after injection.

- Can a study be initiated in children with DMD?
- Can the study be initiated in adults with DMD?
- Is additional information or data required to initiate the study in children, or in adults?
Case Study #7

You wish to use a 3D printer to make a hand-held surgical retractor for use in the OR, because the printer app allows manufacture of subject-specific (unique) tools tailored for use in rare pediatric patients with structural defects.

• Can this be done without IRB approval?

• Can this be done without FDA approval?

• What is the role of the hospital Medical Device Committee?

• Can the 3D printer process be allowed for use in children?

• What are the implications for: Institutional liability; App manufacturer liability; Need to inform subjects in the surgical consent process
Case Study #8

Actual Case: Single Subject IND

- 3 month old child with macrophage activation syndrome and severe pancolitis with massive protein losing enteropathy
- Activating mutation in NLRC4 gene with supra-physiologic IL-18 levels (IL-18 exceeded validated measurement) as well as high IL-1β
- 5th child in the world diagnosed with NLRC4 mutation at the time of diagnosis (June 2015)
- Only partial response to anakinra/cankinumab (IL-1β blockade), infliximab (TNFα blockade), cyclosporine and vedolizumab (T-cell blockade), large doses of steroids, and TPN
- Dr. Ed Behrens, CHOP division head of rheumatology consulted and suggested an experimental IL-18 blocker, Tadekinig alpha, manufactured by a Swiss biotech company, AB2Bio
Case Study #8

Single Subject IND, Continued

• Confirmation that manufacturer intends to supply experimental drug free of charge for the child
• Study team submitted treatment plan to FDA: FDA granted sIND
• Study team submitted materials (treatment plan + ICF) to IRB: IRB approved the study
• Company shipped drug to IDS along with IB + Pharmacy Manual
• IDS reconstituted drug and study team started SC administration
• Monitoring for side-effects and study compliance implemented
• Patient’s response dramatic: Weaned off all medications and TPN, while maintained on Tadekinig alpha over the past > 1 year
Discussion
Extra Case Study
Extra Case Study

You wish to use an iron ingot in cooking pots to increase iron levels in anemic children in an emerging country.

- Is the ingot a device or a drug?
- Can a research study be done without FDA approval?
- What is the regulatory pathway required, if you wish to treat or mitigate iron deficiency?
- What is the regulatory pathway if you wish to collect feasibility and natural history data of iron deficiency in an emerging country?
- Which regulatory jurisdictions are required prior to study start?
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