

Challenges in the Regulation of Pediatric Clinical Trials

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Challenges in the Regulation of Pediatric Clinical Trials : Outline

- Therapeutic Development
 - Objective
 - Process
- Regulatory Process
 - IND Review
 - Clinical Hold
- Pediatric Studies
 - Ethical Principles
 - Special Protections
 - Regulatory Challenges

Therapeutic Development

- Objective: Drugs (including biologics) that are safe and effective for a given indication
- Process
 - Drug discovery
 - Nonclinical (animal) study objectives:
 - Toxicity, biodistribution, carcinogenicity, proof-of-principle
 - Guide design (including dosing, population, and monitoring) of subsequent Phase 1 study
 - Phase 1 objectives:
 - Safety, tolerability, maximum tolerated dose (MTD), pharmacokinetics, (and activity / efficacy, if feasible)
 - Guide dosing and monitoring in subsequent Phase 2 studies
 - Phase 2 objectives:
 - Determine dose, route, regimen, population, endpoints, and estimated magnitude of effect
 - Guide design of subsequent confirmatory (Phase 3) studies
 - Phase 3 objectives:
 - Evidence of efficacy and safety to support a marketing application (New Drug Application (NDA) or Biologics Licensing Application (BLA))

Regulatory Process

Investigational New Drug application (IND)

- Review Team
 - Project Manager
 - Chemistry, Manufacturing, and Controls (CMC)
 - Nonclinical Pharmacology / Toxicology
 - Clinical
 - Others (e.g., statistics, epidemiology, patient representative)
- Objective: FDA's primary objectives in reviewing an IND are, in all phases of the investigation, to assure the safety and rights of subjects ... (21 CFR 312.22(a))
- Clinical Hold
 - A clinical hold is an order issued by FDA to the sponsor to delay a proposed clinical investigation or to suspend an ongoing investigation (21 CFR 312.42 (a)).

Regulatory Process

Clinical Hold: FDA may place a proposed or ongoing Phase 1 investigation on clinical hold if it finds that (21 CFR 312.42(b)):

- (i) Human subjects are or would be exposed to an unreasonable and significant risk of illness or injury;**
- (ii) The clinical investigators named in the IND are not qualified ...;
- (iii) The investigator brochure is misleading, erroneous, or materially incomplete;
- (iv) The IND does not contain sufficient information ... to assess the risks to subjects of the proposed studies.**

Pediatric Studies: Ethical Principles

- Children are a vulnerable population because they are not able to give true informed consent. Therefore,
 - Study adults unless it is “scientifically necessary” to study children.
 - Assess whether studies in adults would be relevant, ethical, feasible, and substantially accomplish the objective(s) of the study.
 - If study of children is scientifically necessary, consider initial study of older children, who are better able to give informed consent.
 - Regulations provide “Additional Safeguards for Children in Clinical Investigations” (21 CFR 50.50 – 50.56; Subpart D)

Pediatric Studies: Subpart D

50.50: IRB duties: In addition to other responsibilities assigned to IRBs ..., each IRB must review clinical investigations involving children as subjects covered by this Subpart D and approve only those clinical investigations that satisfy the criteria described in 50.51, 50.52, or 50.53 ...

Pediatric Studies: Subpart D

- 50.51 Clinical investigations not involving greater than minimal risk
- **50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects.**
- 50.53 Clinical investigations involving greater than minimal risk and no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subjects' disorder or condition. ... The risk represents a minor increase over minimal risk.
- OCTGT believes that gene therapy trials generally have more than a minor increase over minimal risk. Therefore, 50.51 and 50.53 generally do not apply to gene therapy trials.

Pediatric Studies: Subpart D

- **OCTGT regulates gene therapy trials in children with consideration of the principles of 21 CFR 50.52.**
- **50.52 Clinical investigations involving greater than minimal risk but presenting the prospect of direct benefit to individual subjects ... may involve children as subjects only if the IRB finds and documents that :**
 - (a) The risk is justified by the anticipated benefit to the subjects; ...**
- **To provide evidence of the prospect of direct benefit (or the anticipated benefit), OCTGT often asks IND sponsors to provide proof-of-concept data from nonclinical and / or previous human studies.**

Pediatric Studies: Subpart D

- **50.54 Clinical investigations not otherwise approvable that present an opportunity to understand, prevent, or alleviate a serious problem affecting the health or welfare of children.** If an IRB does not believe that a clinical investigation ... involving children as subjects meets the requirements of 50.51, 50.52, or 50.53, the clinical investigation may proceed only if:
 - (a) The IRB finds and documents that the clinical investigation presents a reasonable opportunity to further the understanding, prevention, or alleviation of a serious problem affecting the health or welfare of children; and
 - (b) The Commissioner of Food and Drugs, after consultation with a panel of experts in pertinent disciplines ... and following opportunity for public review and comment, determines ... [that specific conditions are met that allow the study to proceed.]
- If a gene therapy study is not approvable under 50.52, OCTGT does not refer the study for consideration under 50.54. OCTGT believes that such a referral for consideration should come from outside of FDA (e.g., from the IND sponsor or from an IRB).

Regulatory Challenges in Pediatric

Clinical Trials : For the sponsor

- Minimize risks while maintaining prospect of direct benefit and acceptable risk-benefit ratio
 - What constitutes sufficient evidence of a prospect of direct benefit (i.e., proof-of-concept (POC) data)? Should nonclinical POC studies be replicated by independent groups?
 - What is the appropriate study population? Is there an adult population that would be sufficiently informative, with an acceptable risk-benefit ratio?
 - How to determine the starting dose?
 - Consider available nonclinical data (e.g., NOEL and NOAEL) and previous human experience with the product or related products.
 - What study procedures (e.g., MRI, lumbar puncture) are acceptable?
 - Consider the risk of the procedure, the benefit (if any) of the procedure to the subject, and the value of the resulting data (benefit of generalizable knowledge).

Regulatory Challenges in Pediatric Clinical Trials : For the sponsor

- For pediatric studies, OCTGT asks the sponsor to describe the following:
 - how the study meets the requirements of Subpart D
 - why the study of children is scientifically necessary

Regulatory Challenges in Pediatric Clinical Trials : For the FDA

1. When is it appropriate for a pediatric study to be a first-in-man study for a new experimental gene therapy?
2. If adults must be studied to provide initial evidence of safety before proceeding with a study in children, how many adults must be studied?

Regulatory Challenges in Pediatric Clinical Trials : For the IRB

- To what degree do IRBs defer assessment of the science and/or ethical/human subject protection issues to other entities (e.g., FDA, RAC)?
- How do IRBs determine whether early stage gene or cell transfer studies have a prospect of direct benefit?
- How do IRBs help investigators, participants, and their families avoid a therapeutic misconception when communicating risks and anticipated benefits?

Public Workshop on Cell and Gene Therapy Clinical Trials in Pediatric Population

November 2, 2010

Bethesda, Maryland

The goal of this workshop is to gather information from stakeholders regarding best practices related to cell and gene therapy clinical trials in pediatrics including: evaluating these novel therapeutic products prior to initiating pediatric clinical studies, identifying and minimizing risks associated with the administration of cell and gene therapy products in pediatric studies, obtaining informed consent and assent, and conducting continuing review and oversight of cell and gene therapy products in pediatric studies.

Public Workshop on Cell and Gene Therapy Clinical Trials in Pediatric Population

November 2, 2010

Bethesda, Maryland

To register, contact:

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