Prospect of Direct Benefit in Pediatric Clinical Trials
Grand Hyatt Washington
1000 H St NW • Washington, DC 20001
March 29, 2019

Meeting Agenda

Children are a vulnerable population who cannot consent for themselves and therefore require additional protections when participating in clinical research. The National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research met in the late 1970s and made recommendations that led to the establishment of protections for children promulgated in federal regulations. These regulations require that, with rare exceptions, children must have some prospect of direct benefit when participating in research that involves more than a low level of risk. Over the last 40 years, medical science has evolved and pediatric drug development programs have become more complex. An increasing social and legal imperative exists to include children in research to generate an evidence base for their treatment.

This expert workshop, convened under a cooperative agreement with the U.S. Food and Drug Administration, will discuss how direct benefit should be defined in the context of contemporary clinical trials. Concepts such as pediatric extrapolation, the appropriate use of non-human data, applicability of biomarkers to reflect clinical benefit, and the ethics of conducting studies in children when alternative strategies like modeling and simulation are applicable will be explored. The goal of this meeting is to formulate expert opinion on a definition of prospect of direct benefit that includes relevant practical considerations to ensure that pediatric clinical research is ethical and collects adequate data to inform the use of therapeutic products in the pediatric population.

9:00 a.m.  Welcome & Introductions
Gregory Daniel, Duke-Margolis Center for Health Policy

9:05 a.m.  Opening Remarks from FDA

9:15 a.m.  Why Does Prospect of Direct Benefit Matter in Pediatric Clinical Trials?
Moderator: Gregory Daniel

Objectives:

- Discuss the ethical and regulatory requirements for enrolling pediatric patients in clinical trials, based on the paradigm that studies must offer a prospect of direct benefit or be “low” risk.
- Provide a brief overview of how the concept of prospect of direct benefit fits into broader efforts to advance the development of pediatric therapeutics and impacts the timing and the design of pediatric clinical trials.

Presentation: Prospect of Direct Benefit as Defined in 21 CFR 50, Subpart D, the Additional Safeguards for Children in Clinical Investigations

- Donna Snyder, U.S. Food and Drug Administration
**Presentation:** *Prospect of Direct Benefit and Challenges Incorporating the Concept into Clinical Trials*

- Steven Joffe, University of Pennsylvania Perelman School of Medicine

**9:45 a.m. Session 1: Characterizing Prospect of Direct Benefit**

*Moderator: Gregory Daniel*

**Objectives:**
- Explore the concept of the prospect of direct benefit and why it is important to establish for pediatric clinical trial participants.
- Discuss how the severity of the illness and the availability of alternative treatments affect judgments about the prospect of direct benefit.

**Presentations:**
- Nancy King, Wake Forest University
- Jonathan Kimmelman, McGill University

**Lead Reactants:**
- Steven Joffe, University of Pennsylvania Perelman School of Medicine
- Gigi McMillan, U.S. Food and Drug Administration Pediatric Oncology Drug Advisory Committee
- Donna Snyder, U.S. Food and Drug Administration

**11:00 a.m. Break**

**11:15 a.m. Session 2: Prospect of Direct Benefit and Pediatric Extrapolation**

*Moderator: Gregory Daniel*

**Objective:**
- Discuss the concepts of scientific necessity and the prospect of direct benefit in the context of pediatric extrapolation of efficacy from adult data and the impact on timing of studies and study design.

**Presentation:**
- Robert "Skip" Nelson, Johnson & Johnson

**Lead Reactants:**
- Lynne Yao, U.S. Food and Drug Administration
- Anne Zajicek, National Institutes of Health
- Lainie Ross, University of Chicago

**12:00 p.m. Lunch**
1:00 p.m.  **Case Study 1: Use of Nonclinical Models as Proof-of-Concept to Support Pediatric Clinical Trials**  
*Moderator: Mark McClellan, Duke-Margolis Center for Health Policy*

**Objectives:**
- Discuss the strengths and limitations of various nonclinical models used to support proof-of-concept.
- Explore what type of information is needed from nonclinical models to support the prospect of direct benefit when collecting data in adults is not feasible or will significantly delay product development in pediatric patients.

**Presentation:**
- Wendy Halpern, Genentech

**FDA Case Presentation:**
- Kathleen Donohue, U.S. Food and Drug Administration

**Lead Reactants:**
- Jackye Peretz, U.S. Food and Drug Administration
- Forbes "Denny" Porter, National Institutes of Health
- John Lantos, Children’s Mercy Hospital

1:50 p.m.  **Case Study 2: Challenges in Designing Pediatric Pharmacokinetic Studies to Offer a Prospect of Direct Benefit**  
*Moderator: Mark McClellan*

**Objectives:**
- Discuss challenges with establishing dosing when a trial must be designed to offer a prospect of direct benefit to the pediatric participant.
- Discuss alternative approaches to the design of pharmacokinetic studies to maximize the prospect of direct benefit, and when alternative methods, such as modeling and simulation, are appropriate.

**Presentation:**
- John van den Anker, Children’s National Health System

**FDA Case Presentation:**
- Melanie Bhatnagar, U.S. Food and Drug Administration

**Lead Reactants:**
- Albert "AJ" Allen, Eli Lilly
- Peter Adamson, Children’s Hospital of Philadelphia
- Dionna Green, U.S. Food and Drug Administration

2:40 p.m.  **Break**
2:55 p.m.  Case Study 3: Endpoints and Duration of Pediatric Clinical Trials and Prospect of Direct Benefit

*Moderator:* Mark McClellan

**Objectives:**
- Discuss the prospect of direct benefit when studies focus on biomarker rather than clinical (or surrogate clinical) endpoints.
- Discuss the implications for prospect of direct benefit when short-term studies are conducted in participants with chronic diseases.

**Presentation:**
- Dave Wendler, National Institutes of Health

**FDA Case Presentation:**
- Melanie Bhatnagar, U.S. Food and Drug Administration

**Lead Reactants:**
- Susan Kornetsky, Children’s Hospital Boston
- Jonathan Davis, Tufts Medical Center
- John Alexander, U.S. Food and Drug Administration

3:45 p.m.  Session 3: Synthesis Discussion and Next Steps

*Moderator:* Mark McClellan

**Objective:**
- Discuss the next steps for defining the prospect of direct benefit that allows for the ethical conduct of pediatric clinical trials while facilitating the availability of therapeutic agents for children.

**Lead Reactants:**
- Barbara Bierer, Brigham and Women’s Hospital & Harvard Medical School
- Robert Truog, Harvard Center for Bioethics
- Susan Weiner, Children’s Cause for Cancer Advocacy
- Donna Snyder, U.S. Food and Drug Administration

**Open Discussion**

4:30 p.m.  Closing Remarks and Adjournment

Mark McClellan

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