Prospect of Direct Benefit in Pediatric Clinical Trials

Discussion Guide

Introduction
Congress amended the Food, Drug, and Cosmetic Act (FDCA) in 1962 in response to public outcry for stronger drug regulation after a series of catastrophes including infant deaths from diethylene glycol poisoning in sulfanilamide elixir and birth defects from maternal exposure to thalidomide. The amendment required informed consent for participation in clinical trials, that drugs be deemed safe and effective before marketed to the public, and that drugs not tested in children carry a statement recommending that they not be used in children. Ultimately, this legislation that was originally intended to protect children had the unintended consequence of discouraging the conduct of pediatric-specific clinical trials and preventing children from receiving the therapeutic benefits it was designed to provide.1

In 1978, the National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (National Commission) in their Report and Recommendations on Research Involving Children proposed changes to this paradigm by establishing a new ethical framework to encourage the conduct of scientifically and ethically sound pediatric clinical research. The recommendations within this framework, codified within 21 CFR 50, Subpart D as “Additional Safeguards for Children in Clinical Investigations,” provide criteria for ensuring the ethical conduct of pediatric clinical investigations while also characterizing children as a vulnerable population because they cannot themselves provide informed consent to participate in research. Though a crucial first step to help ensure that research in children meets certain ethical standards, these recommendations were ultimately unsuccessful in increasing enrollment within pediatric clinical trials.

Since then, an increase in pediatric clinical research has been driven in large part by the Best Pharmaceuticals for Children Act (BPCA) of 2002 and the Pediatric Research Equity Act (PREA) of 2003. BPCA provides incentives to companies for conducting pediatric studies and PREA authorizes the U.S. Food and Drug Administration (FDA) to require pediatric studies of drugs and biologics. Both pieces of legislation have been relatively successful in encouraging pediatric clinical trials. As of May 2018, they have helped contribute to the approval of more than 730 labeling changes by the FDA for medications prescribed to children.2 However, off-label prescribing of therapeutics not approved for pediatric populations remains persistently high, accounting for 90 percent of prescribing in the Neonatal Intensive Care Unit (NICU) and 42 percent of prescribing in all hospitalized children.3,4 Given that children may require different dosing regimens or respond differently to drugs compared to adults, such prescribing carries risk and can potentially result in serious or fatal side effects.5 Data about the safety and efficacy of treatments for pediatric populations obtained through appropriately designed clinical studies is crucial for protecting children from the risks of morbidity and mortality associated with exposure to therapies that may be unsafe or ineffective in children. Such studies must be scientifically rigorous and ethically sound in order to expedite the availability of treatments for pediatric populations.
The generation of evidence on the use of medical products in pediatric populations is hampered by challenges associated with defining and measuring the prospect of direct benefit. Federal regulations for the conduct of clinical research in children specify that, with rare exceptions, children should be enrolled in clinical studies only when the risks are low or the research offers a potential for direct benefit for the individual study participant. An extensive body of literature exists on the characteristics of low-risk research for individuals who cannot provide informed consent. However, less analysis has been completed with respect to which benefits of research participation qualify as direct benefits, or to when an intervention given in the context of a clinical trial should be viewed as offering a prospect of direct benefit. To advance the design of ethical and high-quality pediatric clinical trial protocols, researchers, reviewers, and regulators must reach consensus on the appropriate definition and application of the concept of prospect of direct benefit.

In order to enhance trial design and support therapeutic development for this vulnerable patient population, the Robert J. Margolis, MD, Center for Health Policy at Duke University, under cooperative agreement with FDA, is convening this expert workshop to discuss how prospect of direct benefit should be defined and considered in the context of contemporary clinical trials. This workshop will explore 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 potentially applicable.

Establishing the Parameters of Direct Benefit
Several legal, regulatory, and ethical parameters should be considered to fully assess and establish the prospect of direct benefit in pediatric populations. For those interventions or procedures that pose more than a minor increase over minimal risk to pediatric populations, 21 CFR 50, Subpart D assigns responsibility to Institutional Review Boards (IRBs) to ensure the following:

- Risk is justified by the anticipated benefit to the subjects;
- Relation of the anticipated benefit to the risk is at least as favorable to the subjects as the that presented by available alternative approaches; and
- Adequate provisions are made for soliciting the assent of the children and permission of their parents or guardians (as set forth in Section 50.55).

It should be noted that no definition for prospect of direct benefit is offered in federal regulations. However, bioethicists who have conducted research on the subject propose that the nature, probability and magnitude, and clinical context of the anticipated benefit be included as dimensions of the definition.

Past research stipulates that the nature of the anticipated benefit accruing to study subjects be directly associated with the tested intervention, stating that direct benefit to subjects should be defined as “arising from receiving the intervention being studied.” Other research emphasizes the scientific necessity of an intervention and the impact it can have on the prospect of direct benefit for enrolled subjects. Researchers have proposed that reviewers consider the likelihood that direct benefit will accrue to any given subject as well as the magnitude and duration of the anticipated benefit. This determination could, in part, be supported by results pertaining to the effectiveness of the intervention in nonclinical studies. Finally, researchers and IRB reviewers may also consider different clinical contexts such as the availability of other therapeutics and the acuity of disease when assessing the anticipated benefits and potential risks associated with the proposed clinical intervention.
In this workshop, introductory presentations and Session 1 will highlight the challenges with defining and measuring prospect of direct benefit in the context of modern approaches to clinical trial design. Stakeholders will be asked to consider the following questions to help guide discussion and expand upon general principles that can both safeguard pediatric patient populations while also enabling more innovative approaches to clinical studies.

Session 1 Discussion Questions:
1. Does the level of evidence needed to support a prospect of direct benefit differ based on disease severity and available alternative therapies?
2. Has our understanding of prospect of direct benefit changed since the National Commission issued their recommendations on research involving children in 1978?
3. When is the likelihood that a child will experience benefit so doubtful that we should not be willing to say a prospect of direct benefit exists?
4. How does prospect of direct benefit differ from demonstrating direct benefit?
5. How does direct benefit differ from collateral benefit?
6. How do we avoid promoting a “therapeutic misconception” in pediatric clinical trials?

Trial Design, Data Collection Approaches, and the Prospect of Direct Benefit
In order to enroll children in trials, sufficient proof-of-concept for prospect of direct benefit is needed to justify exposing children to known (and unknown) risks of an intervention. Researchers may be able to use existing, reliable sources of data to reduce the need for conducting trials in the pediatric population or to supplement existing data collected in pediatric trials in a way that enhances the prospect of direct benefit for trial participants (for instance, modeling and simulation to predict dosing).

Through a presentation in Session 2 and a series of case studies, this workshop will explore the potential promise of novel sources of clinical and nonclinical data for improving the pediatric clinical research enterprise. Specific discussion questions are included below for participants’ consideration.

Extrapolation of Adult Data
By extrapolating efficacy data from adult studies, the efficiency and successful completion of pediatric trials can be increased. If sufficient data exist to support pediatric extrapolation, adult data may be useful in the conduct of pediatric clinical trials even before adult clinical trials reach completion. Depending on the degree of pediatric extrapolation considered permissible, pediatric trials may be limited to studies collecting pharmacokinetic and/or pharmacodynamic (PK/PD) and safety data or might include the collection of efficacy data. The level of data needed in pediatric patients should be carefully considered to limit enrollment of pediatric patients in unnecessary or overly burdensome pediatric studies.

Session 2 Discussion Questions:
1. How are the concepts of scientific necessity and prospect of direct benefit interrelated? From an ethical perspective, if pediatric extrapolation is appropriate, should pediatric studies be limited to data needed to support safety and dosing? What if efficacy studies in pediatrics could be completed sooner without data from adults and are the pediatric studies ethical if more burdensome to children?
2. Is it possible to make a determination that pediatric extrapolation is acceptable prior to completing adult studies? Can pediatric studies be designed to run concurrently with adult studies and still have sufficient prospect of direct benefit?

3. If we have doubts about our ability to extrapolate, and we anticipate differences in efficacy between pediatric patients and adults, do we need some adult human efficacy data to support prospect of direct benefit or can pediatric studies be initiated based on nonclinical proof-of-concept once we have adequate human data to support safety and dosing?

Use of Nonclinical Data
Nonclinical or in vitro data to support proof-of-concept are generally required to initiate clinical studies. When the disease exists in adult populations, it is preferable that additional adult data are collected prior to initiating pediatric clinical trials to further support preliminary efficacy. In some cases, due to either nonexistence or rarity of the disease in adults, adult efficacy information is unavailable and nonclinical models may be the only source of proof-of-concept information. The strength of these nonclinical models will determine whether it is acceptable to allow study of the product in children. Importantly, the characteristics of nonclinical animal model data necessary to establish a sufficient prospect of direct benefit vary with the severity of the disease and the adequacy and availability of alternate treatments.

Case Study 1 Discussion Questions:
1. If the disease only exists in pediatric patients, how should nonclinical models be used to support proof-of-concept and prospect of direct benefit in the pediatric population? In what situations might human data from healthy volunteers be informative?
2. How, if at all, does the utility of nonclinical models that demonstrate improvement in a biomarker differ from the utility of nonclinical models that demonstrate improvement in a clinical manifestation of the disease?
3. In what situations may an in vitro model be used to support proof-of-concept?
4. Assuming a serious disease with limited therapeutic options, are data to support proof-of-concept for a product in a nonclinical model of the disease sufficient to support the prospect of direct benefit and allow enrollment of pediatric patients, if an adult population with the disease exists?

Use of PK/PD Data
Clinical pharmacology information derived from PK/PD studies is vital for helping to identify appropriate doses in pediatric populations. Dosing in adults can be determined by exploring single and multiple doses through dedicated PK/PD studies. However, PK/PD studies are usually short-term and may include subtherapeutic doses that would not offer a benefit to pediatric patients. It is imperative that studies to collect PK/PD data in pediatric patients are carefully designed to collect the data needed to support future pediatric studies while offering a prospect of direct benefit. Adaptive study designs should be considered when appropriate. Furthermore, PK/PD data collected in adults to support effective dosing have potential applications for modeling an effective dose in children. In some instances, dedicated PK/PD studies in pediatric patients may not be needed if modeling and simulation approaches are deemed appropriate, though known limitations of modeling and simulation approaches should be considered when assessing their applicability.
Case Study 2 Discussion Questions:
1. What are strategies for designing dose-ranging PK studies in pediatric patients that offer a prospect of direct benefit?
2. Do considerations for prospect of direct benefit differ if extrapolation of efficacy from the adult population is acceptable (i.e., when the objective of the PK study is to identify the pediatric dose with an exposure similar to that in adults)? Might a single dose offer a prospect of direct benefit?
3. What are the considerations for ensuring prospect of direct benefit where the objective of the PK study is focused on safety and tolerability?
4. To what extent can we rely on modeling and simulation to identify an optimal pediatric dosage?
5. Discuss the need for adding an extension study to a single dose PK study to ensure the prospect of direct benefit. Is a seamless transition to the extension with minimal break in dosing necessary to ensure prospect of direct benefit?

Clinical Endpoints and Duration of Clinical Trials
Choosing outcome measures is an important consideration for designing clinical trials and determining clinical endpoints. Today, biomarkers are often used in clinical research to predict disease progression and treatment response. Based on a presumed impact on the progression of the disease, a change in a biomarker may be interpreted as clinically meaningful. Well-characterized biomarkers can be used as clinically meaningful endpoints that are likely to predict clinical benefit. Still, not all biomarkers are useful in the prediction of clinical benefit, and consequently may have limited utility in supporting prospect of direct benefit determinations. To offer clarity, FDA has released guidance on the formal qualification of biomarkers as drug development tools, though data on validated pediatric biomarkers are currently limited and further investigation is needed.

Another consideration in the design of studies for pediatric patients is determining whether the studies are of sufficiently long duration to offer a prospect of direct clinical benefit. This is particularly relevant with respect to the conduct of clinical trials designed to help pediatric patients manage chronic diseases since benefit from treatment may only manifest over time.

Case Study 3 Discussion Questions:
1. In clinical studies involving pediatric patients with a chronic disease, what study design issues should be considered to ensure the prospect of direct benefit for products that are intended for chronic use?
2. Does a change in an exploratory biomarker of a disease constitute benefit in the context of a pediatric clinical trial or should the trial include a change in a clinically meaningful outcome?
3. If the biomarker is “reasonably likely” to predict a clinically meaningful outcome based on a strong mechanistic and/or epidemiologic rationale, does a change in the biomarker constitute benefit?
4. Is an extension study necessary to allow continued treatment until a validated surrogate or clinically meaningful outcome has been observed?
Conclusion and Next Steps

The conduct of clinical research in children is critical for the development of therapeutics designed to address diseases that affect the pediatric population. In some cases, children may respond differently to drugs and other medical interventions than adults and can experience serious or fatal side effects from interventions deemed safe for the adult population. This response variability makes off-label prescribing, a common practice due, in part, to a lack of clinical evidence to support the use of pediatric therapeutics, potentially risky. Off-label prescribing may also prevent children from receiving the most effective therapeutics for their condition. More data about the safety and efficacy of treatments for the pediatric population, obtained through clinical study, can reduce the risk of morbidity and mortality associated with exposure to therapies that may be unsafe or ineffective in children.

The efficient conduct of pediatric clinical trials has the potential to increase and expedite the availability of pediatric therapeutics, which currently lags behind the development and availability of adult therapeutics for the same conditions. To generate a robust evidence base for the use of pediatric therapeutics and provide sufficient protections for pediatric subjects, better stakeholder consensus on the appropriate definition and application of the concept of prospect of direct benefit in clinical trials is critical. The utility of alternative strategies, such as pediatric extrapolation, modeling and simulation, and adaptive study designs should be considered as modalities for gathering information to support the prospect of direct benefit for pediatric enrollment in clinical trials and for potentially limiting the burden of clinical trials in the pediatric population. Approaches to defining and assessing the prospect of direct benefit should be developed to encourage scientifically necessary clinical trials and access to therapies for the pediatric population. We anticipate that, during this workshop, a discussion of the concept of prospect of direct benefit will contribute to the development of ethically and scientifically sound pediatric clinical trials that will facilitate the availability of therapeutic agents for children.
4 Luedtke and Buck, “Evaluation of Off-Label Prescribing at a Children’s Rehabilitation Center.”
5 Laventhal, Tarini, and Lantos, “Ethical Issues in Neonatal and Pediatric Clinical Trials.”
8 “CFR – Code of Federal Regulations Title 21.”
9 King, “Defining and Describing Benefit Appropriately in Clinical Trials.”
10 Friedman, Robbins, and Wendler, “Which Benefits of Research Participation Count as ‘Direct’?”
11 King, “Defining and Describing Benefit Appropriately in Clinical Trials.”
12 “Research Involving Children (Focusing on FDA Regulations) – Robert ‘Skip’ Nelson MD PhD.”
13 Sun et al., “Extrapolation of Efficacy in Pediatric Drug Development and Evidence-Based Medicine.”
14 “Research Involving Children (Focusing on FDA Regulations) – Robert ‘Skip’ Nelson MD PhD.”
17 Nelson, “Research Involving Children (Focusing on FDA Regulations)”
18 Food and Drug Administration, “General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.”
20 Food and Drug Administration, “General Clinical Pharmacology Considerations for Pediatric Studies for Drugs and Biological Products.”
21 Food and Drug Administration, “Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry.”
22 Sun et al., “Extrapolation of Efficacy in Pediatric Drug Development and Evidence-Based Medicine.”
23 Kelly et al., “Useful Pharmacodynamic Endpoints in Children.”
24 Bai et al., “Strategic Biomarkers for Drug Development in Treating Rare Diseases and Diseases in Neonates and Infants.”
26 Kelly et al., “Useful Pharmacodynamic Endpoints in Children.”