

Prospect of Direct Benefit in Pediatric Trials: Practical Challenges and Potential Solutions

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Clinical research in pediatric patients is necessary to develop safe and effective medicines for children. US Food and Drug Administration (FDA) human subject protection regulations (21 Code of Federal Regulations 50, subpart D) require that, with limited exceptions, research in children that exceeds a defined level of risk must offer a prospect of direct benefit to the individual child that is sufficient to justify those risks. Growing attention to the merits of initiating pediatric clinical trials earlier in the drug and biological product development process has led the FDA to look more closely at the meaning of the regulatory term prospect of direct benefit. In collaboration with the FDA, the Duke-Margolis Center for Health Policy convened a workshop with leading experts in the fields of biomedical ethics, pediatric clinical research, and pediatric product development, as well as patient representatives, to discuss the FDA's approach to characterizing prospect of direct benefit in the context of scientific advances in product development. Workshop topics included the extrapolation of adult efficacy data to children, use of nonclinical models of disease, use of modeling and simulation to support pediatric dosing, and reliance on biomarkers and surrogate end points in clinical research. Discussion from the workshop is provided herein to communicate the challenges that investigators, industry sponsors, regulators, and institutional review boards face when evaluating pediatric research and to outline several approaches to maximize prospect of direct benefit, minimize unnecessary risks and burden, and facilitate timely access to safe and effective medicines for children.

Ensuring access to safe and effective medicines is essential for the health and welfare of children. Several key legislative steps, such as the Best Pharmaceuticals for Children Act of 2002 and the Pediatric Research Equity Act of 2003, have been implemented to encourage or require, respectively, pharmaceutical industry sponsors to study drug and biological products in children. These studies are necessary to obtain data about a product's safety, effectiveness, and dosing in the pediatric population and to allow

pediatric providers to make evidence-based decisions regarding the use of products in children. To accentuate the importance of obtaining pediatric evidence, one can look to the example of chloramphenicol, an antibiotic found to cause a potentially fatal adverse reaction ("gray-baby syndrome") in neonates and infants because of elevated serum chloramphenicol levels resulting from immature metabolic processes; this reaction was not identified until more than a decade after the product was discovered.^{1,2}

abstract

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Growing recognition of the risks of prolonged “off-label” pediatric use of products approved for adults has drawn attention to the merits of initiating pediatric clinical trials earlier in the drug and biological product development process. Earlier pediatric development may allow faster access to medicines for children but also may expose pediatric trial participants to testing of ineffective or unsafe products that never advance to receive US Food and Drug Administration (FDA) approval. Balancing these concerns requires thoughtful consideration of the ethical principles that guide research involving children.

Academic investigators, pharmaceutical industry sponsors, institutional review boards (IRBs), and regulators have an obligation to ensure that research involving children is scientifically sound and ethically justified. Children should only be enrolled in a clinical trial if the research addresses an important scientific and/or public health question relevant to the health and welfare of children and the objectives of the research cannot be met by enrolling adults capable of consent.³ Given that children are a vulnerable population who cannot consent for themselves, additional regulatory safeguards are in place to protect children involved in research (21 Code of Federal Regulations 50, subpart D [2001/2013]).³⁻⁵ These regulations specify that with limited exceptions, children should not be enrolled in research that exceeds a defined level of risk unless the risks are justified by the prospect of direct benefit to the child and the balance of risk to benefit is at least as favorable as that of available alternatives. In this context, the term “children” applies to neonates, infants, children, and adolescents who have not reached the legal age to consent to treatments or procedures in clinical trials.

Increased attention on the initiation of pediatric clinical trials earlier in

product development has led the FDA to look more closely at the meaning of the regulatory term prospect of direct benefit. The FDA generally has defined prospect of direct benefit based on evidence to support the proof of concept, typically derived from multiple data sources (eg, in vitro mechanistic studies, in vivo studies in animal disease models, clinical studies in adults, or previous studies in children), and on the structure of the study intervention (eg, dose selection and duration of treatment as specified in the protocol). Obtaining evidence from adult clinical trials often is a critical step to inform prospect of direct benefit but determining when enough data are available to inform the potential benefits to consider pediatric trial enrollment can be challenging. In the current landscape of product development, several tools are available for supporting and optimizing prospect of direct benefit and for minimizing research burden in children.

In March 2019, the Duke-Margolis Center for Health Policy, in collaboration with the FDA, convened leading experts in the fields of biomedical ethics, pediatric clinical research, and pediatric product development, as well as patient representatives, at a workshop entitled “Prospect of Direct Benefit in Pediatric Clinical Trials” to discuss the FDA’s approach to characterizing prospect of direct benefit in the context of advances in drug and biological product development that are relevant to pediatrics.⁶ The workshop planning committee selected participants on the basis of a review of key scientific publications, experience from previous workshops involving discussion of medical product development for pediatric populations, and recommendations from academic partners and FDA’s Office of Pediatric Therapeutics to ensure a diversity of subject matter expertise, as guided by the agenda

topics. Topics discussed by the panel included the use of extrapolation of adult efficacy data to children (“pediatric extrapolation”) to limit research burden on children, use of nonclinical models of disease to support prospect of direct benefit, use of modeling and simulation of adult and pediatric pharmacokinetic and/or pharmacodynamic data to optimize pediatric dosing, and use of biomarkers and surrogate end points when assessing the adequacy of the trial’s duration. Here, discussion from the workshop will be shared to communicate workshop attendees’ perspectives on the FDA’s approach to assessing prospect of direct benefit and the implications for investigators, industry sponsors, IRBs, pediatric patients, and their parents or caregivers. Understanding and overcoming the challenges these stakeholders face when developing products for children is essential to improving the quantity and quality of therapies available to pediatric providers and their patients. See Table 1 for a summary of workshop discussion of factors that influence assessment of prospect of direct benefit and tools to support and maximize benefit and minimize burden.

CHALLENGES DEFINING PROSPECT OF DIRECT BENEFIT AND IMPLICATIONS FOR PEDIATRIC CLINICAL RESEARCH

Workshop attendees generally agreed that direct benefit in pediatric clinical research must relate to the health of the individual child participating in the research and must arise directly from the research intervention being studied.⁷⁻⁹ One attendee disagreed with the notion that benefit needs to result directly from the research intervention and suggested that direct benefit in research could be, for example, access to health care for indigent children. Attendees also raised viewpoints expressed by previous commentators, including regard for non-health-related

TABLE 1 Workshop Discussion of Factors that Influence Assessment of Prospect of Direct Benefit and Tools to Support and Maximize Benefit and Minimize Burden

Factors That Influence Assessment of Prospect of Direct Benefit	Tools to Support and Maximize Benefit and Minimize Burden
	Evidence to support the proof of concept
<ul style="list-style-type: none"> • Biological plausibility <ul style="list-style-type: none"> ◦ Scientific justification for the proposed mechanism of action and the expected effect in the condition of interest • Nonclinical data <ul style="list-style-type: none"> ◦ In vitro mechanistic studies ◦ In vivo studies in animal disease models • Clinical data <ul style="list-style-type: none"> ◦ Studies in adults with the condition ◦ Previous studies in adults or pediatric patients with relevant conditions 	<p>In vitro data can provide valuable information about the product's activity, particularly for studies conducted using cells or tissues derived from patients with the condition of interest</p> <p>In vivo data obtained by using an animal disease model can provide insight into the product's impact on disease pathophysiology and can help guide dosing decisions for a clinical trial</p> <p>Pediatric extrapolation of adult efficacy data to children can reduce the amount of data needed in children and allow for less burdensome pediatric trials</p>
	Structure of the study intervention
<ul style="list-style-type: none"> • Dosing justification <ul style="list-style-type: none"> ◦ Evidence to support that the proposed dosages for study are likely to have the intended treatment effect • Trial duration <ul style="list-style-type: none"> ◦ Proposed trial duration is long enough for participants to experience a potential treatment effect 	<p>Modeling and simulation of adult and/or pediatric pharmacokinetic/pharmacokinetic data to identify a pediatric dose based on predicted exposure-response relationship</p> <p>PBPK modeling incorporating underlying physiologic parameters and product-specific information to predict the dose-exposure relationship</p> <p>Adaptive trial design to allow for dose exploration and optimization within the context of a trial designed to offer prospect of direct benefit</p> <p>Consider treatment duration decisions made in clinical practice</p> <p>Measure clinically meaningful or validated surrogate end points when possible</p>

PBPK, physiologically based pharmacokinetic.

benefits, such as economic, psychosocial, and kinship, as direct benefits.¹⁰ In general, attendees believed that although such “collateral” benefits of research are important to acknowledge, they cannot be construed as direct.⁸

Precisely what constitutes a prospect of direct benefit was more difficult to define. Workshop attendees agreed that the level of certainty required for determining that a prospect of direct benefit exists is not commensurate with the more rigorous standards required for confirming a product's efficacy. One attendee remarked that phase 3 trials rarely present problems in terms of offering prospect of direct benefit and, along with several attendees, emphasized that early-phase trials are the most problematic. Early-phase trials typically focus on safety, tolerability, and dosing rather than efficacy, generally providing less data to support the potential for benefit. Attendees expressed concern that overstating potential benefits in early-phase research may increase

the risk for therapeutic misconception when research participants fail to distinguish between research and clinical care.⁷

Some commentators have defined prospect of direct benefit as the mere possibility of realizing a direct benefit through participation in research,¹¹ whereas others have asserted that for prospect of direct benefit to exist, a higher and more defined probability of improvement in how the child feels, functions, or survives must exist.¹² Others have used a “reasonable person” standard, considering whether a reasonable parent acting in the best interest of his or her child would allow his or her child to participate in the clinical research after weighing the benefits and risks of participation.⁷ Several attendees highlighted the reasonable person approach, noting that although regulators have a responsibility to ensure scientific standards exist to support initiation of pediatric clinical trials, parents and children consider trial participation in the context of their own

experiences and IRBs are in place to make independent determinations in the context of their communities.

Workshop attendees agreed that whether an intervention offers prospect of direct benefit is separate from whether that prospect of benefit is of sufficient probability, magnitude, and type to justify the risks of the intervention in the context of the child's condition and alternative treatment options, emphasizing that children should not be placed at a disadvantage by participating in research. One attendee highlighted that the severity of the condition or lack of effective treatment alternatives does not increase the likelihood of benefit in research but agreed that unmet medical need influences the degree of uncertainty that may be tolerated when weighing the evidence for potential benefits and risks. See Tables 2 and 3 for a summary of workshop attendees' points of general agreement and differing viewpoints, respectively, regarding the definition of prospect of direct benefit.

TABLE 2 Defining Prospect of Direct Benefit: Points of General Agreement Among Workshop Attendees

- Benefit relates to the health of the individual child enrolled in the study (eg, how the child feels, functions, or survives).
- Direct benefit arises directly from the research intervention being studied and accrues directly to the individual child enrolled in the study.
- The level of certainty required for determining that a prospect of benefit exists is not commensurate with the rigorous standards for confirming efficacy.
- The anticipated benefit needs to adequately justify the risks in the context of the child's condition and alternative treatment options.

Identifying scientific criteria for assessing prospect of direct benefit has implications for regulators for determining when pediatric clinical trial initiation is appropriate. Workshop attendees agreed that collecting preliminary efficacy and dosing information first in adults is reasonable, but they acknowledged that for situations in which obtaining adult data would be unfeasible (eg, conditions that only affect children), uninformative (eg, conditions that differ substantially between adults and children), or unethical (eg, because of unjustified risks), reliance on less robust data to support prospect of direct benefit may be necessary and justified.

SCIENTIFIC NECESSITY AND EXTRAPOLATION OF ADULT EFFICACY DATA TO LIMIT RESEARCH BURDEN ON CHILDREN

Before initiating a pediatric study, consideration should be given to the scientific necessity of collecting data in children and whether tools, such as pediatric extrapolation, might reduce the amount of data needed and allow for less burdensome pediatric clinical trials. According to federal regulation,

extrapolation (the science of which is evolving) of adult efficacy data to children is permissible for pediatric product development programs if the course of the disease and the product's effects are sufficiently similar in pediatric and adult populations.^{13,14} The degree to which investigators, industry sponsors, and regulators can rely on adult efficacy data will direct the type and quantity of evidence needed in children.

If efficacy can be extrapolated from adults, then randomized controlled pediatric trials may not be needed. Pediatric studies could be limited to an open-label collection of safety and dosing information, thereby reducing the research burden on children. Workshop attendees acknowledged that devising a product development program that relies on pediatric extrapolation involves a degree of uncertainty regarding the ability to extrapolate and the potential efficacy in adults. The potential for extrapolation is initially inferred through an understanding of the pathophysiology and natural history of the condition along with evidence of similar responses to treatment. Adult studies are then designed with

attention to pediatric development (eg, ensuring the trial efficacy end points are applicable to both adults and children) and pediatric studies are designed to obtain the information needed to mitigate the remaining uncertainty. Several attendees agreed that pediatric studies in these programs can begin as soon as data exist to support a sufficient prospect of direct benefit to justify the risks, often running concurrently with the adult studies (eg, after preliminary efficacy and safety data are available in adults but before completion of phase 3 adult trials).

Consideration also should be given to whether data can be leveraged from other sources (eg, previous clinical trials in adults or pediatric patients with a related condition or a related product) to make inferences regarding the target pediatric population and potentially reduce the amount of new data required.¹⁵

NONCLINICAL DATA TO SUPPORT PROSPECT OF DIRECT BENEFIT

Nonclinical data frequently are used to support the proof of concept for initiating human clinical trials. Workshop attendees acknowledged that for pediatric diseases for which adult efficacy data cannot be collected, nonclinical data may be the only information available to support prospect of direct benefit for a pediatric trial. Nonclinical data can be obtained from several sources. In vitro data can provide valuable information about the product's activity, particularly for studies conducted by using cells or tissues derived from patients with the condition of interest. In vivo data obtained by using an animal model of the disease can provide insight into the product's impact on disease pathophysiology and can help guide dosing decisions for a clinical trial.

When adequately designed, studies in nonclinical disease models can

TABLE 3 Defining Prospect of Direct Benefit: Differing Viewpoints Among Workshop Attendees

- A benefit is possible
 - Any chance for direct benefit is enough to qualify as a prospect of direct benefit.
- A benefit is likely
 - A higher and more defined probability of benefit must exist to qualify as a prospect of direct benefit.
- A reasonable parent standard
 - A prospect of direct benefit exists if a reasonable parent acting in the best interest of his or her child would allow his or her child to participate in the research after weighing the likelihood of a potential benefit against the potential risks.

contribute valuable information for product development. One workshop attendee commented that nonclinical effectiveness information often is not adequately vetted and suggested that confirmatory nonclinical studies should be performed and evaluated with the same rigor as confirmatory randomized controlled trials in humans. Selecting a suitable model and ensuring adequate sample sizes, use of blinding, and appropriate endpoint selection are critical to ensure the data are interpretable. Many nonclinical models have limitations and are not reliable surrogates of the complex human condition, so the ultimate value of the model is grounded in its relevance to the question(s) the study is designed to address.¹⁶

The acceptability of using nonclinical data as evidence to support prospect of direct benefit for the initiation of pediatric clinical trials is evaluated within the context of the disease, the nature of the investigational treatment, and the strength and applicability of the nonclinical data. During the workshop, the FDA shared 2 product examples (Myozyme [alglucosidase alfa] and Brineura [cerliponase alfa]) for which the agency relied on nonclinical data to support prospect of direct benefit for first-in-human pediatric trials. The conditions evaluated (ie, infantile-onset Pompe disease and late-infantile neuronal ceroid lipofuscinosis type 2, respectively) cause substantial childhood morbidity and early mortality. The products are both specific enzyme replacements for the deficient enzymes underlying the disease.^{17,18}

The utility of nonclinical data for supporting prospect of direct benefit exists on a continuum. An animal model that demonstrates a change in a clinical manifestation of a disease with study treatment may be the most relevant for supporting prospect of direct benefit. Changes in a disease biomarker also may be used,

particularly if the biomarker can be correlated with a clinically meaningful change in the disease. Nevertheless, biomarker-based evidence is virtually always weaker than evidence based on clinical endpoints. Similarly, *in vitro* evidence rarely is used as the sole evidence to support prospect of direct benefit but can contribute to the weight of evidence. Consistency in demonstrating a treatment effect across several nonclinical models augments the evidence to support prospect of direct benefit. Nonclinical toxicology data, including data from juvenile animals when necessary, also are important to assess the potential risks of treatment of the range of pediatric ages to be studied. When appropriate, relevant toxicology endpoints can be incorporated into studies conducted in animal disease models.¹⁹

MODELING AND SIMULATION TO INFORM PEDIATRIC DOSING

For a pediatric trial to offer a potential benefit to participants, evidence is needed to support that the dosing used in the trial is likely to have a clinical effect. Clinical pharmacology information derived from pharmacokinetic or pharmacokinetic/pharmacodynamic evaluations is critical for dose-finding in pediatric populations.^{20,21} Understanding how pharmacokinetic measures (ie, parameters such as volume of distribution and clearance that reflect the body's processing of the product) are linked with pharmacodynamic properties (ie, the product's effects on biomarkers or clinical outcomes for safety and efficacy) allow predictions for dosing to provide the optimal clinical response (exposure-response). For adults, this information often is derived from dedicated single- or multiple-ascending-dose pharmacokinetic or pharmacokinetic/pharmacokinetic studies. These dedicated studies are typically

short-term, are designed solely to collect pharmacokinetic and pharmacodynamic and some safety and tolerability data, may include subtherapeutic doses, and are not necessarily expected to provide a clinical benefit.^{22,23} Conducting similar pharmacokinetic and pharmacodynamic studies in pediatric patients poses challenges when assessing prospect of direct benefit. Rarely, a single-dose study might offer prospect of direct benefit if clinical benefit is anticipated after 1 dose, such as a single dose of an analgesic to treat acute pain. In situations in which a clinical benefit is not anticipated after 1 dose, an open-label extension study to allow continued product administration may be proposed to offer prospect of direct benefit, although workshop attendees questioned whether an extension study is appropriate if a potentially therapeutic dose has not been identified and if the extension is not otherwise scientifically justified.

Workshop attendees noted that in some circumstances, a single-dose study solely intended to collect pharmacokinetic and/or pharmacodynamic data without an expectation for clinical benefit may be allowable in children if existing safety information is available to characterize the risk of a single dose as sufficiently low (in regulatory terms, as imposing at most a "minor increase over minimal risk"). Such studies must be limited to children with, or at risk for, a disorder or condition (ie, the studies cannot be performed in healthy children), and collection of the information must contribute to generalizable knowledge about that disorder or condition.

Modern advances in clinical pharmacology may limit the need to conduct dedicated pediatric pharmacokinetic and pharmacodynamic studies to support dosing for pediatric participants. Mathematical modeling and

simulation strategies using pharmacokinetic and/or pharmacodynamic data collected in adults and/or children may be used to identify a dose for pediatric trials on the basis of predicted exposure-response.²⁴ Physiologically based pharmacokinetic modeling is useful because it integrates underlying physiology and product-specific parameters to predict the dose-exposure relationship.^{24,25} The extent to which modeling and simulation can be relied on varies on the basis of the pharmacologic properties of the drug, the maturation of the physiologic systems responsible for drug disposition, the disease process, and the amount and quality of data available to inform the model.^{24,25}

Modeling and simulation may be most effective when used to identify a starting pediatric dose and then to refine the dose by using pediatric pharmacokinetic and/or pharmacodynamic data collected within the context of an adaptive study design. For example, a prospectively planned interim analysis of exposure and/or response data can allow for dose exploration and optimization within the context of a clinical trial designed to offer prospect of direct benefit. With proper planning, these studies can be designed without undermining the validity or integrity of the clinical trial.²⁶

A population pharmacokinetic approach is commonly used in pediatric product development, which allows for sparse blood sampling from each study participant, thereby reducing the risks and burden of blood sampling to obtain pharmacokinetic data in pediatric participants.^{27,28}

BIOMARKERS AND SURROGATE END POINTS WHEN ASSESSING ADEQUACY OF TRIAL DURATION

Pediatric study participants should receive a study product for

a sufficient length of time to make achieving the anticipated clinical benefit a reasonable possibility. The characteristics of the condition, including what is known about the chronicity of the disease and disease progression in children, are important to consider when assessing the adequacy of the study duration for supporting prospect of direct benefit. These determinations should reflect considerations similar to those made for treatment duration in clinical practice.

Workshop attendees agreed that outcome measures to assess whether the study drug is benefitting the individual child and to support judgments about prospect of direct benefit in subsequent studies should be included in a trial, although the measures do not need to be positioned as the primary end point(s). For studies that are not designed to assess a clinically meaningful outcome in how the child feels, functions, or survives, clinical benefit may be measured as a response to a validated surrogate end point. For a validated surrogate, strong evidence exists that an effect on the surrogate predicts clinical benefit. When measuring clinically meaningful or validated surrogate outcomes is not possible, attendees suggested that unvalidated surrogate measures, including biomarkers, may be assessed as proxies for prospect of direct benefit. These may be useful in justifying the conduct of subsequent trials but should not be mistaken for direct measures of clinical benefit.

Workshop attendees discussed a hypothetical randomized placebo-controlled 12-week study in pediatric patients ≥ 6 years of age with a chronic condition. Attendees were asked to opine on whether the 12-week study duration assessing an impact on a biomarker deemed reasonably likely to predict clinical benefit would be adequate to support prospect of direct benefit. Attendees grappled to draw firm conclusions

without real-life context and wrestled with an envisaged line between prospect of direct benefit and questions of continued product access, particularly if a child was responding favorably. Several attendees voiced concerns that 12 weeks would not be long enough to meaningfully impact the chronic condition, and that trial participation would not benefit the pediatric patients if only a transient impact on their disease occurred. Others expressed opposing opinions, noting that the 12-week study may present a reasonable benefit-risk balance for pediatric participants.

DISCUSSION

Although consensus on how to interpret prospect of direct benefit was not reached during the workshop, the discussion was invaluable for shedding light on the challenges that investigators, industry sponsors, regulators, and IRBs face when evaluating pediatric research. Attendees acknowledged that for product development involving both adults and children, a brief window exists during which industry sponsors can initiate pediatric clinical trials before the potential for off-label prescribing in children (after adult approval) adversely affects the feasibility of conducting pediatric studies. Workshop attendees felt that timely initiation of pediatric product development could be achieved while still upholding the regulatory standards for protecting children in research. All attendees agreed that when appropriate, tools such as pediatric extrapolation, pharmacokinetic and pharmacodynamic modeling and simulation, and adaptive trial designs should be used to limit research burden on children. Using these tools also can streamline pediatric development, facilitating earlier access to safe and effective medicines for children.

The FDA's approach to defining prospect of direct benefit was generally agreeable to workshop attendees. In addition to evaluating all available data to support the proof of concept, the prospect of direct benefit needs to be considered in the context of the study protocol to ensure the enrolled pediatric participants may experience a benefit that is sufficient to justify the risks of the intervention when considering the alternative treatment options. Allowing some regulatory flexibility when assessing prospect of direct benefit was considered reasonable in favor of providing pediatric patients and parents or caregivers opportunities for considering trial participation in the context of their own experiences and values. Attendees highlighted the "reasonable parent" approach, suggesting a focus on what a scrupulous parent would intentionally subject his or her child to in the interest of doing what is best for the child. Attendees thought that such a parent would be more skeptical of a study that relies on nonclinical data or surrogate end points, although attendees agreed that reliance on such information is reasonable in certain circumstances.

Meaningful engagement with parents was deemed critical in this approach. A patient representative at the workshop noted that for a parent or caregiver, hearing the word benefit

will evoke an emotional response centered on a hope for cure and urged investigators, industry sponsors, and IRBs to explore how to optimally communicate research uncertainties so that parents and older children can develop a realistic understanding of the risks and potential clinical benefit of a study.

CONCLUSIONS AND RECOMMENDATIONS

Assessing the balance of potential benefits and risks in pediatric research is complex and relies on scientific, clinical, and moral judgment. The Duke-Margolis Center for Health Policy, in collaboration with the FDA, convened an expert workshop to discuss challenges characterizing prospect of direct benefit in the context of specific advances in pediatric product development. The discussion of topics provided herein provide clear examples of approaches to minimize unnecessary risks and burden on children, maximize prospect of direct benefit for pediatric study participants, and facilitate timely access to safe and effective pediatric medicines.

When developing drug and biological products for children, industry sponsors and pediatric investigators should (1) consider the scientific necessity of the planned pediatric

studies and whether pediatric extrapolation of adult efficacy data could be used to limit research burden on children, (2) establish a compilation of evidence to support the biological plausibility and proof of concept for use of the product in the targeted condition, (3) use advances in clinical pharmacology and adaptive trial designs to identify an appropriate dose for pediatric studies and to minimize the volume and frequency of pharmacokinetic blood sampling, (4) create a study protocol that takes into consideration treatment duration and clinical outcomes that are relevant in clinical practice, and (5) work with patient communities, IRBs, and regulators to create programs that optimize benefit, minimize risk and burden, and carefully convey the potential benefits and risks to patients and parents or caregivers. Thoughtful consideration of these factors will ensure that children benefit from the progress in medicine that is driven by scientific research while still safeguarding children from research risks.

ABBREVIATIONS

FDA: Food and Drug Administration

IRB: institutional review board

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