Plan and Design with the Child in Mind: Global Pediatric Clinical Trials Network Recommendations and Insights for Sponsors of Pediatric Research

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Duke Clinical Research Institute | PEDIATRICS

INTRODUCTION

"Dance So That Others May Walk." That was the slogan inviting people across the United States to help fund polio treatment and research in 1934 through a series of fundraising "birthday balls" in honor of famous polio survivor, President Franklin Delano Roosevelt. Over the course of the next two decades even more communities raised funds for research, making the famous polio vaccine field trials of 1954 possible. More than a million children participated in those trials, and when the vaccine proved successful, pharmaceutical companies and governments worked together quickly to make the vaccines available to all children, regardless of their ability to pay. Today, polio is nearly eradicated with only 33 cases reported globally in 2018.

This success story is still relevant to those looking to overcome the hurdles of pediatric research today. It's the story of everyone—government, industry, patients, communities, clinicians, and researchers—coming together to address seemingly insurmountable challenges. That same spirit of collaboration is driving organizations such as the U.S. Food and Drug Administration (FDA), the Duke Clinical Research Institute, and biopharmaceutical and medical device sponsors to overcome roadblocks in pediatric clinical research and, ultimately, improve and save lives. This spirit of collaboration is also at the center of the establishment of the Global Pediatric Clinical Trials Network, an FDA-sponsored research network led by the DCRI, which aims to support efficient pediatric clinical trials by: developing scientific and operational infrastructure; fostering collaborative networks; sharing knowledge and engaging stakeholders.

The challenges of conducting pediatric clinical research today remain significant. We do not know enough about how drugs work in children, in large part because families are reluctant to participate in research. But that is not where the story ends. Behind the story of low clinical research enrollment are numerous causes as well as numerous pragmatic solutions. When we plan and design pediatric research with the needs of infants, children, adolescents, and their families in mind, solutions emerge and pediatric research moves forward.

This paper reflects a year's worth of qualitative research examining the perspectives of industry sponsors of pediatric clinical research conducted by the Duke Clinical Research Institute on behalf of the Global Pediatric Clinical Trials Network. The insights we gleaned from interviews, focus groups, and workshops helped inform our overall recommendations.

The barriers reported by sponsors were not surprising:

- Sites are reluctant to get involved with pediatric research because of a lack of incentives and the significant burden of conducting trials in children.
- Sponsors face challenges aligning study feasibility and regulatory requirements.
- Study assessments and procedures are often too burdensome for children and families.
- Providers frequently prescribe off-label drug use to children, making study enrollment and randomization difficult.
- Especially for rare diseases, the population of eligible participants may be too small to allow for regulatory targets for recruitment.
- Patient-reported outcomes need to be designed specifically for children.

But what might be surprising is that many of these problems boil down to three common solutions. We recommend that sponsors consider:

- Collaborating early and often with the new constellation of clinical research stakeholders, including patients and their families
- Making wise use of data, including real-world sources of information and registries
- Fostering engagements early and often with regulators and sponsors, ensuring alignment at the beginning of the development process

We will explore these three solutions in the hopes that it spurs further conversation, research, policy reflection, and movement toward more pediatric drug labeling. The recommendations that follow are intended for industry sponsors of clinical research; however, all stakeholders can benefit from thinking about how these solutions apply to their work and how to facilitate more connections to move the pediatric clinical research ecosystem forward.

BACKGROUND AND METHODOLOGY

The Duke Clinical Research Institute was awarded a grant from the FDA in 2017 to establish a coordinating center for the Global Pediatric Clinical Trials Network. The network supports efficient pediatric clinical trials by: developing scientific and operational infrastructure; fostering collaborative networks; sharing knowledge; and engaging stakeholders.

Recognizing that many industry sponsors struggle to meet their obligations under the Pediatric Research Equity Act, which requires pediatric studies for certain drug and biological products, the Duke Clinical Research Institute decided to investigate sponsors' perspectives and share our recommendations to advance pediatric research. In collaboration with Industry Standard Research, a marketing research firm specializing in the pharmaceutical and biotechnology industry, we conducted qualitative research with U.S.-based biopharma stakeholders between August 2018 and May 2019. This qualitative research was conducted in three ways:

- 10 in-depth phone interviews with decision-makers at biopharmaceutical companies that have PREA requirements
- A 3-day online focus group with 41 participants from decision-makers at pharmaceutical or biotechnology companies (April 2019)
- Half-day, face-to-face, customized educational workshops with 6 different sponsor companies focused on their challenges with PREA and our recommended solutions. (September 2018-May 2019)

All participants for these activities were screened to ensure they worked for a biopharma sponsor, in an applicable department, and had direct experience with pediatric trials in the United States.

We created a discussion guide for interviews, which we then modified for the focus groups based on our experiences in the interviews. Agendas for the customized educational workshops varied by each company's need and were based on documents shared about drugs currently in development. Before workshops we reviewed all documents, identified the top 3 challenges and then developed customized solutions to discuss during the workshop. All participants were assured of confidentiality.

SOLUTION #1: COLLABORATE WITH ALL STAKEHOLDERS

Too often, studies are designed without thinking carefully about the needs of patients or practicing physicians. In pediatrics, this is an especially crucial issue as adult trials cannot simply be retro-fitted for children. To plan and design with the child in mind, sponsors of pediatric clinical research should collaborate early and often with a multitude of stakeholders—including pediatric patients and their families.

As one participant from the online focus group said:

"We need to get more patient/parent-focused in our research designs. If we make it impossible for a parent to hold down a job they rely on for health insurance because they need to sacrifice days over days for weeks (or sometimes years) on end to take their child to study visits, we are not getting their participation. ... Engage the patients and parents so that they want to participate."

This sentiment echoes what we heard from other focus group participants. Nearly 40% of focus group respondents cited the inability to convince a parent to enroll a child as a top challenge to patient enrollment in pediatric studies. To overcome this challenge, we recommend that clinical research sponsors collaborate with families and caregivers and consider more patient- and parent-focused research designs that incorporate:

- Gathering parent/child and practicing physician input into study endpoints, assessments/questionnaires, and visit schedules
- Organizing schedules and inclusion/exclusion criteria to maximize participation
- Minimizing blood draws and other study procedures that are not standard of care while still gathering the necessary data to make the right comparison
- Focusing on educating parents during the consent/assent process

- Paring down the study to the minimum data required
- Asking patients what endpoints are important to them
- Designing questionnaires in child-appropriate language
- Weighing the pros and cons of study requirements carefully such as whether or not a placebo-controlled study is really needed or asking whether there are enough patients to meet requirements.

Pediatricians and clinical research sites are another source of invaluable collaboration when planning a study. Sites can help balance protocol content and complexity against what is actually feasible to execute. For example, sites can help think through how to create simple inclusion/exclusion criteria so that patients are more likely to be screened by site staff, which will increase enrollment.

While not all pediatricians take part in clinical trials and may have limited knowledge and experience, medical consortiums composed of pediatricians experienced in pediatric trials can help review draft protocols as well as help identify potential principal investigators.

Finding patients, especially for clinical trials of rare diseases, is another significant challenge. Nearly 50% of focus group respondents cited the universe of potential patients as a top challenge to patient enrollment in pediatric studies. To overcome this challenge, sponsors should go where patients are and collaborate closely with patient groups and care providers.

Discussing this challenge, a participant from an in-depth interview said:

"Particularly for orphan indications, unmet need is high and there is generally great interest in investigational therapies. Patient advocacy groups are generally well-organized, motivated, and collaborative."

Patient groups can do more than help identify patients, however. They can provide meaningful input to make pediatric studies more patient-friendly and they can help increase acceptance within the patient community of not just the study but also study findings. Sponsors should consider forming patient advisory groups by therapeutic area, indication, or study to collect feedback on protocol design, specifically inclusion/exclusion criteria, endpoints, visit schedule, and assessments. These groups should ensure that advisors represent caregivers from different developmental life stages.

In addition to patients, families, sites, and advocacy groups, non-traditional collaborators can help move pediatric research forward. For example, collaborations with other sponsors, research networks, and registries can lead to shared master protocols, multi-sponsor registries, and more effective communications with regulators. While multi-sponsor collaborations can be difficult, common registries or natural history studies can be one way to generate real-world evidence that supports labeling. Established pediatric networks can help sponsors conduct more efficient and effective pediatric research.

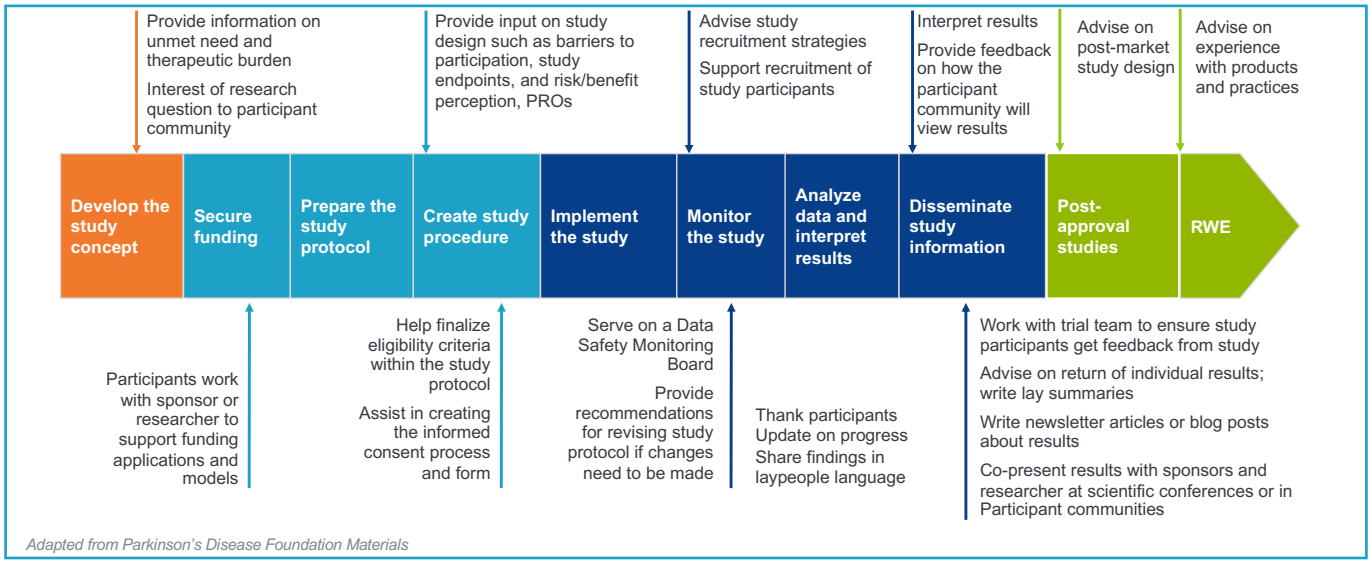
EASING PARTICIPANT BURDEN IN PEDIATRIC RESEARCH:

Broaden inclusion/exclusion criteria to enhance feasibility.
Enroll children in more than one clinical trial at a time.
Combine protocols (e.g., for oral and IV formulations) when possible for greater efficiency and to overcome enrollment challenges.
Combine multiple drugs in one study.
Use opportunistic study designs that align with standard of care.

Finally, it is important also to collaborate with contract research organizations (CROs), academic research organizations (AROs), and other consultants that might have valuable "been there, done that" experience. CROs and AROs can support a sponsor's pediatric development programs and should be evaluated based on a strong pediatric track record, specialized staff, therapeutic expertise, and strong partnerships with academic advisors and patient partners. Small companies, in particular, can rely on ARO/CRO resources to run the clinical trials, and on external consultants (like pediatricians) for input into protocol design and execution. Sponsor companies should consider using external practitioners that have active research programs in the disease area and a corresponding clinical practice as consultants.

One interview participant said: "CRO [selection] is not just [based on] experience in that particular therapeutic area ... you need to read the guidance and all that stuff, but the devil's always in the details. and I think if you have either a colleague or consultant or CRO that can walk you through, it makes all the difference."

The DCRI's Research Together program helps facilitate participant engagement at every step of the research process.



SOLUTION #2: MAKE WISE USE OF DATA

If industry sponsors carefully evaluate the data they have and employ it in a way that helps answer important clinical questions, they may find that they have enough data to help design more efficient clinical trials; support findings from clinical trials; or possibly avoid the need for additional clinical trials. The FDA is showing more willingness to accept methods other than traditional clinical trials, including registries and other sources of real-world evidence,[1] pharmacokinetic modeling and simulation, and extrapolation from adult data, in decisions regarding pediatric medications and dosing.[2,3]

"In post-marketing, physicians started to treat pediatric patients with the drug. So, the FDA took this safety data in children, considered the clinical need in light of risk vs. benefit, and made a decision to approve without a formal clinical trial. I can't describe how uplifting this was – it gave me hope that the FDA wasn't just out to haze pharma companies to make it as difficult as possible to get a drug to market," said one workshop participant.

Registries and Other Sources of Real-World Data

Many health care providers continue to prescribe drugs to children off-label. This is especially true for neonates, with 90% of drugs being used without specific dosing and safety information for this vulnerable population.[4] Making use of registries and other real-world sources can help generate pharmacokinetic, safety, and efficacy data that may be instrumental in gaining approval for a particular drug in the pediatric population. A 2017 guidance document[5] from the FDA on the use of real-world evidence to support regulatory decision-making for medical devices indicates that the agency is open to accepting data from these sources. If designed appropriately, these registries could generate regulatory-grade data and help the sponsor determine the necessity, optimal design, and feasibility of future studies.

A registry may also serve as a platform to inform the design and facilitate the conduct of future pediatric trials. The Childhood Arthritis and Rheumatology Research Alliance (CARRA) Registry, for example, collects information about the long-term safety of medications used to treat pediatric rheumatic diseases, as well as side effects and quality of life for patients. As of August 2019, nearly 9,000 patients were enrolled.[6] Registries like CARRA can provide valuable information such as the quality of sites, sites that are more likely to enroll patients in a potential trial, and what to consider in determining inclusion and exclusion criteria. Integrating clinical trials within registries may offer opportunities to avoid duplicative data collection, accelerate time to critical decision-making, and potentially reduce cost.[7]

Registries are a relatively low investment, especially considering the possible benefits. In pre-competitive spaces, multiple sponsors could collaborate on registries so that everyone benefits. It is recommended to start developing a patient registry as early as possible. Consider partnering with the NIH, academic institutions, and/or other sponsors for funding. Registries need IRB-approval and if data generated will be used in support of or in conjunction with an NDA application,

the registry should be set up to be regulatory compliant. The Clinical Trials Transformation Initiative recommends, when designing a new registry, to articulate the purpose of the registry clearly and transparently, define and describe participant characteristics, select clinically relevant data elements, set forth systematic and consistent data processes, and take steps to ensure patient protection.[7] Other options to explore include electronic health records, databases, and patient-reported evidence.

Extrapolation from Adult or Other Data

Extrapolating data from adults or other groups to the pediatric population can streamline drug development and help increase the number of approvals for pediatric use. This approach is based on the assumption that the adult and pediatric populations have similar disease progressions, responses to intervention, and exposure-response relationships.[8]

The FDA endorses extrapolation as a method for pediatric drug development. In 2011, an FDA workgroup conducted a review of 370 pediatric studies representing 166 drug products submitted from 1998 to 2008. Findings from Dunne et al show that new labeling for pediatric use was obtained for 84 products (61 percent) for which extrapolation was used. In those instances, the use of extrapolation resulted in fewer studies and patients needed for pediatric drug development.[8]

It is important to remember that adult data needs to be used in conjunction with supporting pediatric data, such as safety information and pharmacokinetic data for determination of appropriate doses. In the instances mentioned above, a single controlled trial, a single uncontrolled and/or unpowered efficacy trial, an exposure-response trial, and/or a pharmacokinetic study were requested to support extrapolation when it was used.[8]

It is also critical to be specific about what can be extrapolated and the justification for why. The decision should take into account all aspects of the disease in both the adult and pediatric populations, experience with other drugs in the same class and for the same indication, and the validity of the pediatric efficacy endpoints.[8] Reviewing and incorporating literature, clinical registry data, and other existing data sources, can help in building strong, evidence-based cases justifying that extrapolation principles are being met.

Pharmacokinetic Data for Modeling and Simulation

Sometimes direct extrapolation of adult data is inappropriate, considering the significant developmental changes that children undergo. Because modeling and simulation studies take these changes into account, they are more likely to enable the correct assessment of drug exposure in children.[9] Population pharmacokinetic modeling is a well-established methodology in infants and children, and the number of trials using this approach is steadily increasing.[10] Although requiring an investment in time and money, modeling and simulation can ultimately save resources by providing a way to integrate all information gathered on medical products.[11] Creating an appropriate model can not only allow for the accurate prediction and characterization of the drug, but also help in the design of clinical trials by identifying optimal pharmacokinetic sampling time points and dosing regimens.[9]

Several modeling strategies may be used; however, population pharmacokinetic modeling has become a particularly popular and accepted method for explaining variability in drug exposure and response. Data from each individual contributes to the identification of larger trends such as changes in drug exposure with changing age or weight.[11] Population models can also be developed using relatively few observations from each subject, and the resulting estimates can be compared to previous assessments to determine consistency between studies or patient populations. This property of population modeling is particularly attractive for pediatric pharmacokinetic data, where the number of drug concentration measurements obtained per subject may be limited by low overall blood volume and the challenges associated with blood sampling in children. The data can also be compared with those relating to other similar drugs to help assess their potential.[11] It is also important to note that if adult data are available, developing an adult population pharmacokinetic model and scaling it to children may be helpful.

Because data quality is critical for this method, it is important to invest time in ensuring that the data are sound and to accurately and thoroughly describe the development of the population model and the methods used to evaluate data. Pharmacokinetic data should be collected whenever possible to incrementally refine and validate models. Any final report should be descriptive enough to justify and explain the conclusions.[11]

Considerations for Pediatric Clinical Trials

If pediatric trials are needed, there are ways to improve feasibility and enrollment.

Begin planning the pediatric program early. Do not wait until pediatric data are required to begin planning. According to a survey conducted by the Tufts Center for the Study of Drug Development, only one in 11 companies said that they "often" plan pediatric studies in parallel with the corresponding adult program.[4] The adult drug development phase provides an opportunity to develop reliable, validated biomarkers and surrogate endpoints for use in children. It is advisable to seek input from parents and potential participants to ensure endpoints are appropriate and patient-centric. The adult drug development phase also allows for the consideration and development of pediatric formulations such as suspensions or chewable tablets. This is especially critical in younger populations that are more likely to reject medications on the basis of smell, taste, and texture.[12]

Include adolescents in adult trials. Consider enrolling adolescents in adult trials as early as can safely be done. This could provide valuable information on any differences in the drug response for younger patients and help make the case that data can be successfully extrapolated. If there are no scientific issues with an endpoint, also consider parallel trials with even younger (age 0-11) populations. To address the issue of whether children should be dosed to begin with, have a conversation with the FDA and provide justification and expert sources that show the drug is similar in adolescents as in adults and demonstrate a clear effort to enroll children.

Broaden inclusion/exclusion criteria. Negotiate inclusion and exclusion criteria to make them as broad and streamlined as possible. While it is critical in late-phase trials to include only participants who might benefit from the study and exclude those with conditions that might obscure the primary endpoint, those designing early-phase trials often use the same approach for setting criteria. For phase 1 and 2 studies, criteria may be expanded to prevent having an overly narrow population for studies determining pharmacokinetic effect or safety.[13]

Combine protocols. Combine pharmacokinetic trial protocols for greater efficiency. Oral and IV formulations, for example, could be combined into one trial to help overcome enrollment challenges. There are also appropriate situations for studying more than one drug in any given trial.[13]

Use minimally invasive sampling techniques. A significant hurdle to enrolling children in trials is the reluctance of parents to subject their children to additional, and often uncomfortable, procedures. Some protocol requirements even call for blood volumes that exceed the maximum allowable amounts for a child's age and size.[12] In order to minimize burden on the patient, consider the following sampling strategies:

- Sparse sampling uses two to three samples per subject with ultra-low sample volume.
- Scavenged sampling uses samples remaining after lab tests performed as part of regular care.
- Dried blood spot sampling collects miniscule amounts of blood on blotting paper. Its advantages include minimal personnel training, no sample processing, room temperature storage, and simple bioanalytical analysis.
- Opportunistic sampling involves taking extra fluid at the time of routine blood draws.
- Multidrug assays measure several different compounds in the same sample.[14]
- Use of alternative biological fluids such as saliva may also be considered.[10]

SOLUTION #3: ENGAGE WITH REGULATORS EFFECTIVELY

After collaborating with stakeholders and thinking carefully about data choices, a final and crucial recommendation for industry sponsors is to meet early and effectively with the FDA. Too often sponsors perceive their regulatory interactions as fraught and struggle to understand when and how to engage with the FDA, European Medicines Agency (EMA), and other regulatory agencies.

Companies should reframe their engagement as a collaborative effort in which all stakeholders are united in wanting to advance the best therapeutics for children. To do so, sponsors should:

- Start discussions early
- Come to discussions prepared
- Make sure that plans for all regulatory entities are consistent

Many focus group participants cautioned that, among other concerns, the validity of endpoints is often sacrificed to meet aggressive timelines, only to meet resistance from the FDA later. Most participants identified the beginning or end of phase 2 as the ideal time to begin discussions, while some cautioned that discussions should begin even earlier.

One focus group participant said: "Before the drug is put in patients, the trial design and ultimate data generated, including pediatrics, should have FDA buy-in to guide the entire program."

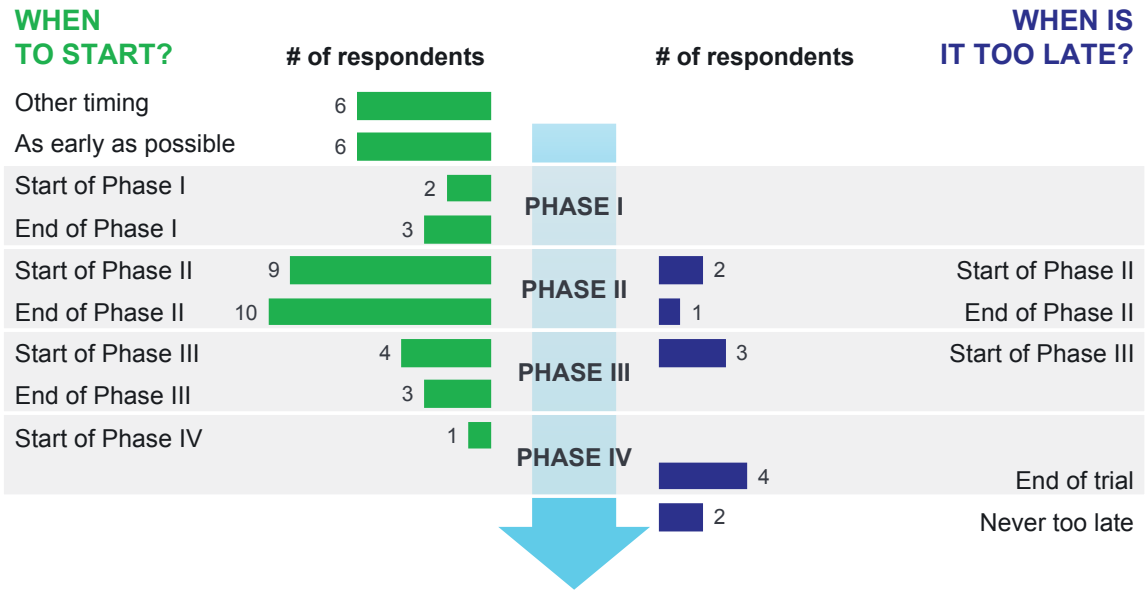
Companies should come to regulatory meetings prepared with specific questions to specific problems identified during the development of an actual strategy. This helps meetings to be more efficient, reduces risks of miscommunication, and avoids the need for multiple meetings. Companies should also find and use existing data, including real-world data, to justify approaches. They should also do research on prior approvals for similar studies and borrow strategies used by other companies. During the discussions, it is important to be specific, efficient, and open to new ideas and suggestions. It is also important to allow time for iteration to ensure that a sponsor does not overpromise on study design.

"Our final plans for pediatric trials have always ended up being completely different from what we set out to do due to requests and negotiations with regulators. Initially we found this frustrating, but in hindsight they were great opportunities for collaborations with health authorities to address needs of pediatric patients," said one focus group participant.

Many companies do not always know to reach out to the FDA's Office of Pediatric Therapeutics. This office is not tied to review divisions and can often help facilitate a common understanding at the agency of what a company wants to accomplish.

When dealing with multiple regulatory entities such as the FDA and EMA, it behooves sponsors to minimize any duplicative work in meeting multiple obligations. Sponsors should start by engaging early and separately with all agencies to better understand any conflicting requirements. It is also important to be consistent in the ideas and evidence presented, as agencies cross-communicate and will raise red flags with each other when there are concerns.

In the online focus group, representatives from companies were asked when in the development process (e.g. phase) is the ideal time for a company to start discussions with FDA/EMA about pediatric study design and when is too late.



CONCLUSIONS

The Duke Clinical Research Institute's commitment to advance the scientific investigation of medical therapies in children begins at the bedside. We know firsthand the limits and risks of providing treatments based only on evidence generated through studies carried out in adults. This research is an extension of that commitment and our desire to help biopharmaceutical companies in their own efforts to advance pediatric research. Just as communities everywhere have addressed critical challenges in the past, the path forward requires stakeholders working together.

Our hope is that our qualitative research will spark further discussion and exploration into best practices for stakeholder collaboration, regulatory engagement, and smarter choices about data collection and use.

Next steps for the Global Pediatric Clinical Trials program include:

- Exploring hurdles at the clinical research site level and addressing them
- Systematically reviewing the best ideas in using real-world data
- Exploring how to leverage registries for innovative research
- Developing master protocols that improve the efficiency and quality of pediatric research
- Engaging caregivers and adolescents in the design of protocols and research process, and providing lay friendly materials to empower families to make informed decisions

We invite you to learn more about the Duke Clinical Research Institute and our ideas for advancing pediatric research globally. For more information visit: DCRI.org or contact us https://dcri.org/contact-us/.

REFERENCES

[1]Cohen-Wolkowiez M, Benjamin DK Jr. Development of Therapeutics for Children – A Tricky Balancing Act. JAMA Pediatrics. 2019;173(1): 18-19. https://jamanetwork.com/journals/jamapediatrics/fullarticle/2714381. Accessed August 5, 2019.

[2]U.S. Food and Drug Administration. Leveraging Existing Clinical Data for Extrapolation to Pediatric Uses of Medical Devices. 2016. https://www.fda.gov/media/91889/download. Accessed August 6, 2019

[3]U.S. Food and Drug Administration. Drugs for Treatment of Partial Onset Seizures: Full Extrapolation of Efficacy from Adults to Pediatric Patients 2 Years of Age and Older Guidance for Industry. 2019. https://www.fda.gov/media/130449/download. Accessed September 12, 2019.

[4]Yen E, Davis JM, Milne CP. Impact of Regulatory Incentive Programs on the Future of Pediatric Drug Development. Therapeutic Innovation & Regulatory Science. 2019. https://www.ncbi.nlm.nih.gov/pubmed/30983385. Accessed August 5, 2019.

[5]U.S. Food and Drug Administration. Framework for FDA's Real-World Evidence Program. 2018. https://www.fda.gov/media/120060/download. Accessed August 6, 2019.

[6]CARRA (Childhood Arthritis and Rheumatology Research Alliance) website. https://carragroup.org/

[7]Clinical Trials Transformation Initiative (CTTI). CTTI Recommendations: Registry Trials. May 2017. https://www.ctti-clinicaltrials.org/files/recommendations/registrytrials-recs.pdf. Accessed June 26, 2019.

[8]Dunne J, Rodriguez WJ, Murphy MD, et al. Extrapolation of adult data and other data in pediatric drug-development programs. Pediatrics. 2011;128(5):1242-9. https://www.ncbi.nlm.nih.gov/pubmed/22025597. Accessed June 27, 2019.

[9]Sampson M, Benjamin DK Jr., and Cohen-Wolkowiez M. Evidence-based guidelines for pediatric clinical trials: Focus on StaR Child Health. Expert Review of Clinical Pharmacology. 2012;5(5): 525-531.

[10]Autmizguine J, Benjamin DK Jr., Smith PB, et al. Pharmacokinetic studies in infants using minimal-risk study designs. Current Clinical Pharmacology. 2014;9(4):350-8. https://www.ncbi.nlm.nih.gov/pubmed/24844642. Accessed August 5, 2019.

[11]Mould DR and Upton RN. Basic Concepts in Population Modeling, Simulation, and Model-Based Drug Development. CPT: Pharmacometrics & Systems Pharmacology. 2012;1(9). https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3606044/#bib46. Accessed August 5, 2019.

[12]Shakhnovich V, Hornik CP, Kearns G, et al. How to Conduct Clinical Trials in Children: A Tutorial. Clinical and Translational Science. 2019;12(3): 218-230. https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6510379/. Accessed August 5, 2019, 2019.

[13]England A, Wade K, Smith PB, et al. Optimizing operational efficiencies in early phase trials: The Pediatric Trials Network experience. Contemporary Clinical Trials. 2016;47. 376-82. https://www.ncbi.nlm.nih.gov/pubmed/26968616. Accessed June 27, 2019.

[14]Laughon M, Benjamin DK Jr, Capparelli E, et al. Innovative Clinical Trial Design for Pediatric Therapeutics. Expert Review of Clinical Pharmacology. 2011;4(5). 643-652. https://www.ncbi.nlm.nih.gov/pubmed/21980319. Accessed August 5, 2019.