PEDIATRIC RARE DISEASE CLINICAL TRIALS: MEDPACE CLINICAL RESEARCH EXPERTS SHARE STRATEGIES FOR SUCCESS

There are over 300 million people worldwide who are living with a rare disease and around 75 percent of rare diseases will affect pediatric patients.

The World Health Organization (WHO) estimates that there are between 5,000 and 8,000 rare diseases worldwide. Rare diseases are estimated to affect more than 300 million people globally. About 80 percent of rare diseases have a genetic basis.[1] Most rare diseases are chronic conditions, and many are clinically progressive and potentially fatal.

The definition of a rare disease varies geographically. In the US, the definition of a rare disease was formed by the Orphan Drug Act of 1983 and is defined as a disease that affects less than 200,000 people in the US. Considering the thousands of different rare diseases that exist, around 30 million people in the US live with a rare disease.[1] In the European Union (EU), a rare disease is defined as affecting fewer than five in 10,000 people.[2] Therefore, a rare disease may impact up to 240,000 people in the EU, but some rare diseases could be found in only a handful of patients. Up to 36 million individuals in the EU have a rare disease.

It is estimated that around 75 percent of rare diseases will affect pediatric patients.[1] Therefore, pediatric rare disease clinical trials are vital to determining the safety and efficacy of medications for children living with a rare disease.

“Pediatric rare disease trials, by combining both the rarity of the rare disease as well as the restricted number of pediatric patients, do highlight some challenges,” said Dr. Gregory Hale, Senior Medical Director, Hematology and Oncology, of the global contract research organization (CRO) Medpace. “There's no single way to design a trial for pediatric rare diseases. A strong communication with regulatory authorities increases your chance of successful outcome.”

In a recent webinar that aired on Rare Disease Day 2022, Dr. Hale described the challenges and key considerations of pediatric rare disease clinical trials. In the same webinar, Tanya Konovalenko, Director, Regulatory Affairs, Medpace, spoke about the regulatory considerations for these trials. The webinar concluded with Kyle Haas, Associate Director, Clinical Trial Management, Medpace, speaking about the operational and study start-up considerations for pediatric rare disease clinical research.

Watch the free, on-demand webinar featuring the experts from Medpace to learn about strategies that can help overcome the regulatory and operational challenges of pediatric rare disease clinical trials.

ASPECTS OF PEDIATRIC MEDICAL RESEARCH

To conduct clinical research with children, it is important to recognize that children are developmentally and physiologically different than adults. In addition, children cannot give consent because they are not at the age of majority. Thus, children are regarded to be vulnerable subjects for research and should have an appropriate proxy to consent for them.

The US Food and Drug Administration (FDA) outlined a basic ethical framework for pediatric clinical trials, which includes the following[3]:

- Pediatric patients should only participate in a clinical trial if the scientific and/or public health objective(s) cannot be met through enrolling participants who can personally give informed consent (i.e., adults)
- Without the prospect of a direct clinical benefit to pediatric patients enrolled in a clinical trial, the risks that children are exposed to must be considered low
- After being enrolled in a clinical trial, pediatric patients should not be put at a disadvantage, either through exposure to excessive risks or by failing to access needed health care

Therefore, pediatric clinical trials should only proceed if the trial does not involve more than minimal risk or, if there is more than minimal risk, there is the prospect of direct clinical benefit to the subject.

CHALLENGES IN PEDIATRIC RARE DISEASE CLINICAL TRIALS

Considering both the rarity of the disease as well as the limited number of pediatric patients, pediatric rare disease clinical research has some unique hurdles. Some key challenges in pediatric rare disease trials were reviewed during the webinar and include the following:

- Rare disorders with few pediatric subjects available for study
- Affected populations can be geographically dispersed throughout the world
- A limited number of research centers and a limited number of physicians who can provide the care that many of these patients need
- Phenotypic diversity within the affected population
- Lack of validated endpoints, outcome measures, tools, instruments and biomarkers (compounded in the pediatric population because additional validation and standardization would need to be done for children)
- Natural history often not well understood
- No precedent for drug development for a specific disease, as many of the trials are the first drug development trial for that specific disease
- Ethical considerations for children
- Special considerations for children, including that the drug effect, dose, disease progression and disease manifestation can be different compared to adults, as children are still growing and have immature organs

Therefore, pediatric rare disease trials still face obstacles, including difficulties in diagnosing the medical condition in small populations.

TRIAL CONSIDERATIONS FOR PEDIATRIC RARE DISEASE CLINICAL RESEARCH

In the webinar, Dr. Hale explained that understanding the rare disease pathophysiology as well as the drug's mechanism of action is important. Also, there must be a standard of evidence to establish safety and efficacy. Therefore, the trials must adhere to regulatory guidelines designed for drug approval. Reliable endpoint and outcome assessments are also vital for pediatric rare disease research. Surrogate endpoints should be considered because the diseases are rare, and the patient populations are small.

"A surrogate endpoint would be some type of biomarker, whether it's a laboratory result, radiograph report or a physical sign that is itself not a measure of a clinical benefit but is reasonably likely to predict the benefit. That sometimes will make a trial easier to run in a more timely fashion. An example of a surrogate endpoint would be cholesterol when looking at the impact of myocardial infarction," explained Dr. Hale.

Also, the natural history of the disease should be described or well known. According to Dr. Hale, natural history studies can be helpful for designing clinical trials, especially if a disease has a very limited drug development history (**Figure 1**). Dr. Hale gave an example of how a natural history study was used as a control that led to the FDA approval of alglucosidase alfa in Pompe disease, a pediatric metabolic disorder affecting the cardiac and skeletal muscle.

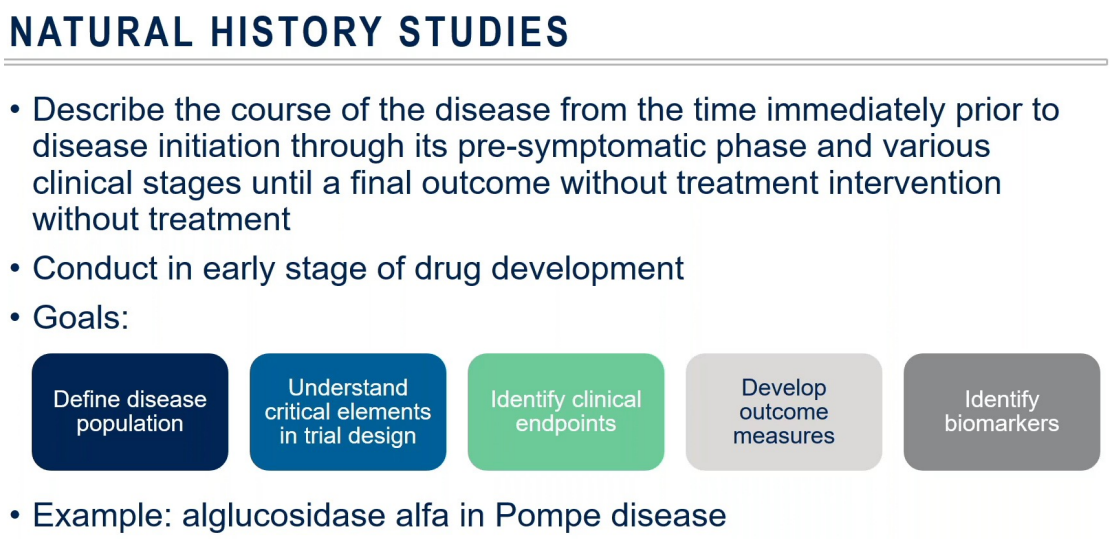

Figure 1: The goals of natural history studies for drug development in pediatric rare disease clinical trials.

"In many cases, the trial is the first trial of a medication designed to treat a disease. However, it's important to note that the natural history will be important in identifying outcome measures, endpoints, as well as biomarker development," said Dr. Hale.

The poor understanding of the rare disease course and the phenotypic diversity of the illness make drug development challenging. Incorporating registry data can help understand the development of the disease and the clinical trial design. Dr. Hale gave examples of things to be cognizant of when thinking about extrapolating data obtained from a registry, and include questions such as: What is the data quality? Is the data complete? Is the diagnosis confirmed? How is treatment documented and over what time period is it? How can the data be used to demonstrate safety or efficacy?

TRIAL DESIGN CONSIDERATIONS

According to Dr. Hale, randomized clinical trials remain the gold standard when possible. Very low patient numbers make the size of most trials in these diseases necessarily small, hence some forms of inferential statistics may be restricted. Small clinical trials with a conventional design may only be able to detect very large treatment effects. In addition, having multiple subgroups within each disease can further decrease sample sizes for analysis.

Furthermore, Dr. Hale said trials must involve key opinion leaders (KOLs) and a knowledgeable regulatory affairs professional who understands both the rare disease and the pediatric aspects. Dr. Hale also encouraged engaging a statistician to help, starting from the trial design stage to establishing endpoints throughout the study. Engaging patients and advocacy groups is also beneficial for conducting pediatric rare disease clinical research.

Adaptive clinical trial designs enable pediatric rare disease trials to be more flexible and efficient. For instance, the trial platform can include multiple investigational treatments with a shared control group. Another example is a single-arm, non-randomized, open-label trial design, which Dr. Hale noted can be used with natural history or registry data as a control arm. Other approaches mentioned by Dr. Hale included a trial design with cross-over or open label extension.

Relaxing the statistical significance level for hypothesis testing is a consideration, but Dr. Hale stressed this should be carefully discussed with a statistician as it may alter the ability to identify a statistically significant difference in the trial.

"Always be in communication with the regulatory agency at every step in your trial development and they can let you know their thoughts," said Dr. Hale. "That will make your path forward to obtain IND [Investigational New Drug] approval much more expeditious."

STATISTICAL CONSIDERATIONS

It is well known that small sample sizes can limit trial design options and the application of inferential statistics. For these reasons, pediatric rare disease drug development should have novel strategies for trial design and statistical strategies.

Enrichment strategies can be used for pediatric rare disease research. Enrichment is defined by the FDA to be "the prospective use of any patient characteristic to select a study population in which detection of a drug effect (if one is in fact present) is more likely than it would be in an unselected population."

Another method includes the use of a control arm receiving a standard of care, which according to Dr. Hale typically requires a natural history study or registry data in the absence of an established standard of care within the indication.

A randomized delayed-start trial can be considered, where subjects are randomized to the same treatment, but some patients get treatment at the start of the trial and others begin treatment after a specified delay. Dr. Hale explained that this trial design allows investigators to separate immediate symptomatic effects from those occurring later on as the disease progresses.

Additionally, a randomized enrichment design with an internal control can be used. "This allows prospective use of any patient characteristic to select a study population in which the detection of a drug effect is more likely, than in the unselected population. So that would allow you also to reach your statistical endpoint, potentially with fewer patients," said Dr. Hale.

REGULATORY CONSIDERATIONS

In the US, the Orphan Drug Act was passed in 1983 to facilitate the development of orphan drugs, which are drugs for rare diseases[4]. In the EU, the European Parliament adopted Regulation (EC) No 141/2000 (the Orphan Regulation) near the end of 1999[5]. This regulation defines the procedure for designation of orphan medicines, as well as the incentives for development and marketing of designated orphan medicines.

During the webinar, Konovalenko outlined the main differences in orphan designation criteria between the US and EU (**Figure 2**).

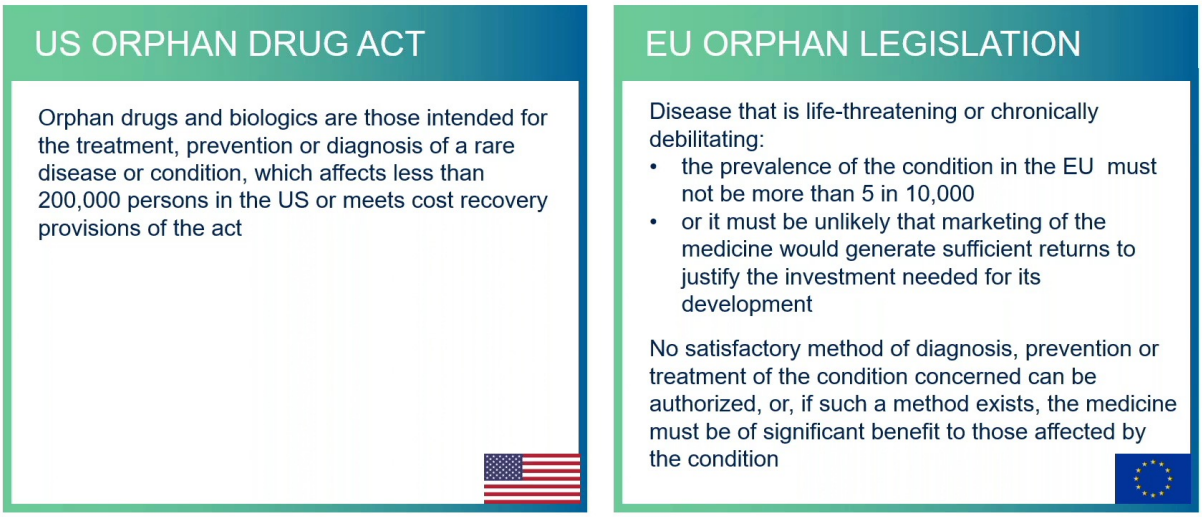

Figure 2: The key differences in orphan designation criteria between the US and EU.

Pediatric legislations have also been established in the US to improve access for safe and effective medicines for children. A company must submit an initial Pediatric Study Plan (iPSP) for a new route of administration, new indication, new dosage form, new dosing regimen or new active ingredient, unless the drug is for an indication that was granted orphan designation[6].

The main pediatric drug development laws in the US are:

- Pediatric Research Equity Act (PREA) of 2003: Requires sponsors to assess safety and effectiveness of new drugs/biologics in pediatric patients — this is initiated by an application for a new indication, new dosage form, new dosing regimen, new route of administration or new active ingredient[7]
- Best Pharmaceuticals for Children Act (BPCA) of 2002: Gives a financial incentive of additional marketing exclusivity to sponsors to voluntarily conduct pediatric studies via a Written Request (WR)[8]
- Title V of FDA Safety and Innovation Act (FDASIA) of 2012: Makes the BPCA and the PREA permanent[9]

In the EU, Regulation (EC) No 1901/2006 (the Paediatric Regulation) was introduced in 2006 to facilitate the development of medicines for children.[10] Applicants must submit a Pediatric Investigation Plan (PIP) to the Paediatric Committee (PDCO) of the European Medicines Agency (EMA) "no later than the completion of adult human pharmacokinetic studies" and requests for a waiver of development have to be justified.[11]

In the webinar, Konovalenko described the main differences in pediatric legislation criteria between the US BPCA, the US PREA and the pediatric legislation in the EU (**Figure 3**).

	US BPCA	US PREA	EU
Development	Optional (written request)	Mandatory	Mandatory
Waiver	NA	3 grounds	3 grounds
Timing	End of phase 2	End of phase 2	End of phase 1
Reward	6 months exclusivity	_	Main: 6 months SPC extension
Orphan	Included	Excluded (except some oncology products)	Included
Biologics	Yes	All	All (biosimilars excluded)
Decision	FDA review division	FDA review division	EMA (PDCO)

Figure 3: The main differences in pediatric legislation criteria between the US BPCA, the US PREA and the EU.

Konovalenko explained that in the EU, a pediatric plan or request for waiver must be submitted to the EMA at the end of Phase I. Additionally, all new medicinal products, regardless of whether orphan designation has been granted, should have a pediatric plan, or a waiver approved by the Pediatric Committee in the EU. On the other hand, a pediatric plan is required at the end of Phase II in the US. Generally, no pediatric plan is needed in the US if the drug is for an indication that has been granted orphan designation.

"Not long ago, patient advocacy and clinician groups in the US had expressed concerns that much needed cancer drugs for children have not been made available in a timely manner. They had suggested that children should be included in all cancer trials unless scientific or ethical rationale would justify their exclusion. This led to the introduction of the [Research to Accelerate Cures and Equity] RACE for Children Act in 2017," said Konovalenko.

As a result, the RACE for Children Act indicates that applications for certain drugs and biologics — including orphan drugs — which could also be a treatment for pediatric cancer, must include an evaluation of the safety and efficacy of the medication in pediatric patients. Therefore, the FDA is authorized to require PREA pediatric studies if a molecular target of a cancer drug for adults is relevant to cancer in children.

It is important to note that the example set by the RACE for Children Act should be extended to other overlooked diseases and all orphan diseases to make sure that every child can equally benefit from the newest available treatments.

An important message from Konovalenko's presentation is that pediatric orphan drug development programs are increasingly multiregional. These programs encounter challenges due to regional differences in pediatric and orphan regulatory requirements, standards of care, medical guidelines and operational practicalities.

"The planning for pediatric development of orphan drugs should be integrated into overall global development, considering regional differences," said Konovalenko. "Waiting to begin planning until adult development has concluded can limit the opportunity to generate meaningful, timely data for the pediatric population battling a rare disease."

EXAMPLES OF OPERATIONAL AND START-UP CONSIDERATIONS BY MEDPACE

According to Haas, country identification and site selection are also crucial factors for patient recruitment. An effort should be made to understand any differences in regulatory or operational processes for multi-country studies. Also, the specific delays or challenges that might be in certain countries at the given time should be identified.

Patient-centric study designs are also welcomed to minimize the burden to the patient and families. Haas explained that strategically planning a positive patient experience to reduce patient and caretaker burden is essential to best positioning the study for effective patient recruitment and retention. Additionally, assessments can be tailored to minimize patient discomfort. Facilitating family travel across small and great distances should be done as well while being as inclusive as possible.

"Our Medpace Patient Concierge Services is our travel group that's able to help book travel, reduce out-of-pocket burden for those families and make sure that they're able to get to the site quickly and efficiently — and that it's as least stressful as possible. And, that we're able to consistently get them to the site, so that they can perform the study procedures that are required," said Haas.

Medpace also aims to assemble a cross-functional team of experts to bring people with different experiences and knowledge together.

"Here at Medpace, our Medical Monitors are integrated with the study team and are able to provide that additional guidance using their expertise. It's really helpful to ensure that whenever we're making a decision, we're looking at it from a cross functional perspective," added Haas.

To address patient recruitment and retention challenges for pediatric rare disease studies, Haas says that identifying and partnering with KOLs as well as patient advocacy groups for community outreach is very helpful. Additionally, building referral networks helps bring in additional patients for screening.

"At Medpace, we have a patient recruitment and retention team. They're able to build a toolkit of materials and patient items that are tailored for pediatrics and rare disease," said Haas.

Haas's key message is that establishing collaborative relationships with key team members is one of the most important things for a pediatric rare disease study. This includes building strong relationships between the sponsor and the CRO, as well as with key site members, KOLs, any other vendors or key study personnel.

To learn more about the strategies to help overcome regulatory and operational challenges of pediatric rare disease clinical trials, register to watch the free on-demand webinar by Medpace.

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FULL-SERVICE CLINICAL DEVELOPMENT

Medpace is a scientifically-driven, global, full-service clinical contract research organization (CRO) providing Phase I-IV clinical development services to the biotechnology, pharmaceutical and medical device industries. Medpace's mission is to accelerate the global development of safe and effective medical therapeutics through its high-science and disciplined operating approach that leverages local regulatory and deep therapeutic expertise across all major areas including oncology, cardiology, metabolic disease, endocrinology, central nervous system and anti-viral and anti-infective.

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