HOW MEDPACE ADDRESSES THE UNIQUE CHALLENGES IN RARE DISEASE CLINICAL RESEARCH

APPLYING 'LESSONS LEARNED', INNOVATIVE THINKING, AND CREATIVE PROBLEM SOLVING

Developing treatments for rare diseases and orphan indications provides a special opportunity to make a truly meaningful, innovative contribution to the field of medicine. Although it is very rewarding to help advance the treatment of conditions with unmet medical needs, such studies also provide special challenges in terms of study design, site identification, patient recruitment, and operational logistics. The unique physiology of such patients often translates into specialized clinical endpoint assessments, which require thorough study team training and thoughtful procedural planning. In addition, safety assessments and laboratory monitoring must often be tailored to ensure adequate and appropriate monitoring of safety in the context of the underlying condition. Rare diseases are often associated with significant patient fragility and mobility issues, so that relatively routine procedures, such as height/weight assessments, blood draws, and imaging studies, often require careful planning to ensure accuracy and minimization of distress and discomfort.

Many of the trials conducted for investigational products with orphan designation involve pediatric patients. The complex nature of conducting rare disease studies, especially studies in a pediatric population, demands that the study team has a thorough medical understanding of the disease, as well as the issues surrounding its epidemiology. In addition, it is important that the team recognizes the vulnerability of the patient population and the ethical considerations related to pediatric and rare disease clinical trials, including a comprehensive understanding of the unique concerns raised by IRBs/ethics committees, Investigators, and parents.

The Medpace team has extensive experience with rare disease and orphan indications, including multiple studies in pediatrics. The following sections describe some of the strategies and creative problem-solving tactics our team has employed to overcome unique challenges associated with conducting these studies.

FEASIBILITY/SITE IDENTIFICATION

By definition, patients with rare conditions are challenging populations to recruit. However, at appropriately selected sites, potential study subjects can be readily pre-identified. Typically, patients with rare diseases are directed to specialized centers, academic institutions, and pediatric hospitals. The Medpace team's experience working with academic groups and pediatric research networks and skillfulness at efficiently resourcing such programs for which subject enrollment and activity may occur at a slower rate across a network of sites, have been fundamental to success in past studies. Additional keys to selecting appropriate investigational sites include: familiarity with the standard medical treatment of the disorder among various regions/demographics, networking with key opinion leaders/academic institutions, and a thorough understanding of the epidemiology and inheritance patterns for the disorder. Ensuring consistency in background care and availability of diagnostic and therapeutic resources across different countries and regions is also important. The Medpace team thoroughly reviews potential sites to ensure appropriate staff resources and facilities as well as adequate experience and training. Academic research clinics often have many demands on time and resources. Because of these demands, providing assistance with start-up process navigation, including development of study-specific recruitment plans and materials, providing detailed checklists for assisting sites with source document development, and training site staff thoroughly regarding the protocol and GCP/GDP practices, are additional tools the Medpace team has employed for study success.

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PATIENT RECRUITMENT

In most cases, the site/practice's database will be the primary source of prospective patient identification. It is anticipated that most patients will be pre-identified, and ultimately "pre-screened" such that once the study is initiated at a site, enrollment can essentially be implemented immediately. Once a site is selected, site-specific recruitment plans are developed and our team works closely with sites to assess potential patients on an individual basis to resolve issues that may hinder patients from participating in the study. Moreover, while patients and families with rare diseases are often highly interested in clinical research, collaboration with patient advocacy groups, can significantly improve study and medication awareness and further enhance site and patient interest and enthusiasm. Such organizations often provide listings of current clinical trials and updates on the medication pipeline and may have associated site networks as well.

Pediatric trials in rare diseases can have particular challenges in recruiting and retention. Specific recruitment challenges in trials involving children and adolescents are related to the unique emotional issues for children with disease, social/family dynamics, as well as practical issues such as scheduling, transportation, drug administration, storage, and compliance. Knowing that regulatory timelines at some academic institutions are often substantially longer than those that use centralized IRBs, the Medpace study team works to develop relationships with the sites as soon as we begin work. This is essential for us to be most informed on the site's regulatory and operational structure in order to assist them in meeting regulatory timelines, identifying and enrolling patients, and capturing the necessary data. Physicians and sites who treat rare disease are often very enthusiastic about new therapies. Based on experience in prior pediatric orphan indications, the enthusiasm of sites and investigators for these studies is often helpful for expediting IRB/EC review and start-up processes and ensuring thorough, accurate prescreening activities.

RETENTION

It is not uncommon for patients with rare conditions to travel very long distances for medical care. Providing patient/caregiver assistance with travel and lodging, if needed, will help ensure patient retention. Medpace has experience establishing such services by working with patient advocacy organizations and/or travel agencies to help families make travel arrangements and minimize out of pocket costs. The Medpace team also has extensive experience on how to address challenges associated with conducting required study assessments while reducing the burden placed on patients and families in terms of time and discomfort. Some examples include: providing a recommended sequence of study procedures to sites to ensure efficiency and establish clear expectations for patients/caregivers regarding the expected length of visits; use of skilled home nursing vendors for conduct of certain study procedures and assessments; and tailoring assessments for minimization of patient discomfort and distress (ie, use of topical anesthetics for blood draws, placement of hep-locked IVs, use of butterfly needles, and reducing blood draw volumes).

ETHICAL CONSIDERATIONS

As studies of rare diseases often involve pediatric patients, it is critical that the CRO team is able to balance the intricate operational, regulatory, and ethical issues associated with conducting the study with an awareness of the inherent concerns often raised by ethics committees (especially in academic centers), clinical specialists, and parents. Pediatric subjects are specialized given their unique and fundamental differences from adults, especially physiological and biological differences, the dynamic changes due to growth and development, their attitudes, perceptions of the world, and their psychological outlooks. The enrollment of pediatric subjects in clinical trials has the additional complexity of family dynamics, legal status, and requirements of informed consent and assent. In addition, the vulnerability of children demands special expertise with regard to pediatric Investigators and awareness of the intricate ethical issues associated with conducting these trials.

Pediatric studies must be carefully designed in order to provide meaningful data to clinicians and minimize risk and discomfort to patients while remaining practical and able to be executed. Potential safety risks such as invasive study procedures, especially those involving sedation or radiation exposure, must be thoroughly justified, including evidence regarding the necessity of such assessments for adequate safety or efficacy monitoring and the infeasibility of alternate assessments. Every attempt must be made to minimize the number of participants and procedures. Blood volumes for laboratory sampling must be monitored to ensure compliance with WHO guidelines, accounting for health status of study patients, as applicable. Fully informed consent must be obtained from the legal guardian and patients should assent to participation as determined by ethics committees or local legal requirements. Communication variability based on age and development should shape the design of assent documents and the conduct of the informed consent process, utilizing pictures, videos, and child-friendly demonstrations to explain procedures to younger children, as appropriate. Incorporation of an open-label extension and use of rescue medications can be used to help justify placebo-controlled designs, facilitating regulatory approval, study enrollment, and patient retention.

In general, studies should be conducted in subjects who directly benefit from participation. Whenever possible, the study IP should be evaluated in an older, more fully mature cohort first followed by evaluation in younger patient cohorts. Unless the risk is minimal or the study will yield information that contributes substantially to the benefit of other children with the disorder, it is difficult to ethically justify the performance of studies in young patients when there is no opportunity for the patient to directly benefit. Finally, independent DMC review of study data serves an important function for ensuring unbiased assessment of the evolving risk vs. benefit profile.

Recognizing the operational and regulatory issues involved in recruiting and retaining patients for rare disease studies, the vulnerability of such patient populations, and the ethical considerations that may arise, Medpace uses our team's broad therapeutic experience and expertise in rare disease and pediatric studies to pre-identify issues and address them before the study is impacted.

REGULATORY SUBMISSIONS

As previously mentioned, sites participating in rare disease and orphan indications are often large academic research institutions and, depending on the specific indication, may include pediatric hospitals. Such sites generally utilize local IRBs/special ECs, which require longer review times.

Successfully implementing regulations and ethical standards into study conduct requires a comprehensive understanding of the unique concerns raised by ethics committees, investigators, parents and patients themselves. Medpace works with the sites selected to ensure they are aware of these specialized needs, as well as strategies to address them.

PEDIATRIC SUBMISSIONS CONSIDERATIONS

Based on Medpace's pediatric experience, EC reviews may prolong timelines if the rigor of their review is unanticipated. For example:

- ECs may involve pediatric experts(if a member is not a pediatric expert)
- ECs will scrutinize patient documents such as ICFs and other patient items
- ECs may request to involve investigator(s) who are experienced in working with children (if the study is not run at a site specializing in pediatrics)
- ECs may require to involve a specific Pediatric Committee in the process

To lower the risk of lengthy negotiations, deficiencies and/or queries, Medpace reviews past experiences with each site and discusses the EC review process and expectations with each Investigator prior to submission. Further, applicable feedback and correspondence from Pediatric Committee, PDCO, will be included with the EC submissions. Preparation of the ICFs are completed during the start-up phase of the trial.

SAFETY MONITORING

Safety monitoring for rare disease clinical studies must take into account the unique physiology of the patient population, including common comorbidities and the interaction of these conditions in the context of the IP's mechanism of action. In addition, in pediatric studies, different age groups are often more susceptible to particular toxicities due to age-related changes in physiology, such as immature liver function and bilirubin metabolism in neonates and fluctuations in gonadal and pituitary hormones in adolescence. Such issues should be carefully considered in order to anticipate potential AEs among patients and ensure rapid detection of safety signals. Safety parameters should address the needs of all cohorts and be interpreted appropriately in the setting of normal physiology. For example, use of creatinine clearance for assessment of renal function may be relatively insensitive in young children and in patients with low muscle mass due to chronic illness. Interpretation of values within the context of additional parameters such as cystatin C levels, BUN, electrolytes, urinalysis, and the urine protein/creatinine ratio, can provide improved sensitivity for detecting changes in renal function. In addition, laboratory and vital sign ranges may need to account for age, sex, and height-adjusted norms, as necessary. Providing simple references in the protocol or study manual for vital sign and physical exam assessments such as blood pressure percentiles as well as guidelines regarding performance of proper measurements (height, recumbent length, head circumference, etc) is often helpful for sites. Automatic calculation of percentiles and z-scores for weight, height, height velocity, and BMI parameters using EDC programming is also helpful for ensuring accuracy of data and avoiding unnecessary queries. The adequacy of the sites' study equipment for these assessments, including appropriately-sized blood pressure cuffs, calibrated scales, and stadiometer equipment should be also be evaluated. If utilized, patient reported outcome assessments should be developmentally appropriate and account for the range of cognitive and communication capabilities among the patient population. The timing and frequency of evaluations must also be considered, balancing adequate monitoring of subject safety with the practical concerns of prolonged study visits and disruptions to work, school, and family schedules. Study-specific laboratory algorithms and alert flagging can be important tools for protecting subject safety by providing guidelines to investigators regarding the need for additional diagnostic evaluation, IP interruption/withdrawal, and/or the use of rescue medications. Supplying guidance to the site regarding management of common background medications in the context of study treatment is also helpful.

A COLLABORATIVE EFFORT

Clinical research in rare disease and orphan indications presents a unique set of challenges that demand innovative thinking and creative problem solving from an experienced team. Over the years, Medpace has amassed scientific, regulatory and operational experts with a passion for clinical development in rare diseases. And because this often includes pediatric studies, our depth of knowledge and experience in working with these special populations further enhances our ability to conduct studies in this area. Medpace brings a depth of experience and expertise that is widely applicable to a variety of clinical studies in rare disease.

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.