Contract research organizations (CROs) and clinical investigative sites are increasingly adopting a patient-centric approach to trial design to address some of the challenges inherent in clinical research.

# Patient-Focused Clinical Trial Design for Rare Diseases Like Duchenne Muscular Dystrophy

Any clinical program has its challenges: from recruiting patients, staying within timelines and handling the inevitable trial amendments, clinical researchers must manage all aspects of the study for the best chance of success. For clinical trials of rare diseases, these challenges can be amplified, particularly because the eligible patient population is so limited.

Contract research organizations (CROs) and clinical investigative sites are increasingly adopting a patient-centric approach to trial design to address some of the challenges inherent in clinical research. That special focus on both finding the right patients to enroll, and making it as easy as possible for them to participate in the clinical trial, can be a key differentiator between trials that meet their endpoints, and those that don't.

"We try and optimize our patient recruitment at Cincinnati Children's and I think this occurs at a lot of other institutions as well," says Dr. John Lynn Jefferies, Director of the Advanced Heart Failure and Cardiomyopathy Programs at Cincinnati Children's Hospital Medical Center. "Obviously, patient recruitment is critical for clinical research; without the subjects, we can't do any meaningful clinical research."

To learn more about patient-focused clinical trial design in the rare disease space, watch this on-demand webinar from Medpace.

## Balancing the Challenges and Benefits in Rare Disease Trials

Since many rare disease indications represent an unmet medical need, the US Food and Drug Administration (FDA) and other regulatory bodies have established programs aimed at incentivising rare disease drug development. For example, FDA's Orphan Drug Act (ODA) allows the regulator to grant orphan status to drugs that serve rare disease patient populations in the US of 200,000 people or less. Drugmakers granted orphan status benefit from tax credits and other financial incentives that help them cover the cost of developing the drug or biologic.

In addition, regulatory agencies have smaller requirements for the number of patients in which a therapy must be tested before it can be considered for approval.

"We're fortunate in the rare disease space that some of the numbers that are required aren't as robust as what we might see in some adult trials which might require six or seven thousand patients to complete a study that can take many years," says Jefferies. "So, we have an advantage where we can recruit a smaller number of patients."

Clinical researchers in the rare disease space must contend not only with a small patient population from which to recruit study participants, but a patient group that may be geographically spread throughout the world.

"Many rare diseases that we care for, such as Duchenne, have epicenters of care and these are known throughout the globe," says Jefferies. "These are the places where most of the research is going to be occurring."

But before the advent of the internet and social media, which allows patients to be their own health advocates and search for clinical trials that they may be eligible to participate in, patients outside of these epicenters of care were at a disadvantage. Jefferies explains that knowledge of ongoing rare disease studies by primary care physicians was often limited, leading to a lose-lose for both patients and trialists trying to meet recruitment goals.

"In the past, patients who were really not seen at centers performing the research would not have access to participation," says Jefferies. "So, without these epicenters of care many patients may just go to their local providers and the local providers maybe only see one or two of these in their entire practice when it comes to rare diseases. It makes it very challenging for them to be up-to-date and aware of clinical investigations."

# What it Means to be Patient-Focused in Rare Disease Research

Now, patient awareness of clinical trials has grown exponentially and CROs are actively working with investigative sites and patient advocacy groups to spread the word even further. But finding patients is just half the battle; even highly-engaged patients face barriers to access in clinical studies.

“I get emails on a daily basis from patients from all over the world that are interested in clinical trials that we’re doing at Cincinnati Children’s,” says Jefferies. “They can get their answers relatively quickly – I can tell them based on what they tell me over the phone whether their child may qualify based on known inclusion and exclusion criteria.”

Once eligible patients are identified, it’s important to make it as convenient as possible for them to participate in the study. The rise in multi-center trials has helped to reduce patient burden when it comes to traveling to sites, giving patients more options for trial participation.

“The future of clinical trials and recruitment is very open and encouraging,” says Jefferies. “The more social media is involved, the more awareness increases. The other great thing is that multicenter trials are becoming more commonplace.

“As technologies continue to improve and become more available, I think the awareness will be more widespread allowing them to prioritize which studies they’d like to participate in moving forward. Recognizing that their child or themselves might be candidates for multiple studies, they can rank order which studies they really want to participate in. You have to remember sometimes that participation in a clinical trial may preclude you from participating in other clinical trials, so this gives the patients the opportunity to be thoughtful about which study they really want to participate in.”

# Patient-Centric Trial Design

According to Michelle Petersen, Senior Associate Director of Clinical Trial Management for clinical contract research organization Medpace, patient input on trial design is a must for making rare disease studies more patient-centric. Endpoints should be chosen not only on the basis of which ones will best assess the efficacy of a therapy, but also on what would be most meaningful to the patients in terms of improving quality of life.

“We do find that getting the patient input on the trial design as well as the informed consent process really helps to give us an idea of what’s going to improve the trial,” says Petersen. “A lot of people are very interested in this feedback but are unsure of how to actually obtain it.”

She suggests engaging a number of key groups to help inform trial design decisions that will ultimately affect patients participating in the study. Petersen emphasizes the importance of patient advocacy groups and attendance at both local and international patient meetings for the rare disease.

But it's not enough to engage with patients only when making study design and protocol decisions. It's imperative that participants – and the rare disease patient community as a whole – be regularly updated on study findings and other important information by way of emails, press releases and webinars. Petersen also says that providing a layperson's summary of results can be helpful in making sure everyone feels included.

"The other key to participation is to ensure that once the patients are found and in the study, we retain them in our study," says Petersen. "From our perspective, burden reduction is critical to keep patients in the study but also to make the study possible for them to participate in in the first place."

Participant burden can be reduced in a number of ways, including having visit window flexibility to allow patients who work during the day to complete their study visit on nights and weekends, and making use of home healthcare services which could eliminate some of these visits altogether. The family of the participant should also be taken into account when establishing support systems, particularly in pediatric trials where parents may have other small children to care for.

But alternative trial designs can also reduce patient burden and improve retention without compromising the quality of clinical data collected during the course of a study. For example, applying a crossover trial design can give all patients access to the investigational therapy, while providing the sponsor with the placebo/standard of care data necessary to accurately compare treatments.

"With rare disease there are often complex endpoints which also reduce the number of centers that are able to participate in the clinical trial," says Petersen. "This means further travel for a lot of subjects which is an increase in burden."

To address this, Petersen suggests sites consider a "hub and spoke" trial design which would still require patients to travel to the main study site for major procedures but allow them to visit local sites for minor procedures. Alternatively, if a study protocol requires collection of patient data at frequent time points, participants could be alternately assigned to only a few of those time points to reduce sample collection burden.

# Rare Disease Patient Experiences in Clinical Trials

As emphasized by both Jefferies and Petersen, hearing from rare disease patients, and their families, is perhaps the best way to ensure that trials are being conducted in a truly patient-focused way. One of those patient stories is that of Beth Woelfel Harvey, a mother of two children whose son, JB, was diagnosed with Duchenne muscular dystrophy (DMD) when he was 16 months old.

In the decade since his initial diagnosis, Harvey and her son have been navigating the complex clinical trial landscape for the rare disease, with JB participating in four studies for DMD. These varied experiences have helped her and her family to identify what's working – and what's not –

in the current clinical trials system, allowing them to provide clinical researchers with valuable feedback and offer advice to other rare disease patients.

“In 2009, when JB was diagnosed, there were no standards of care for Duchenne muscular dystrophy,” says Harvey, who is also the founder and Executive Director of JB’s Keys to DMD, a foundation committed to raising awareness of DMD and supporting patients like JB. “There were three small clinical trials that most neurologists were not even aware of. There were only three companies developing drugs for Duchenne and they were struggling to get funding.

“Now, in 2018, there are standards of care that were even recently revised to keep up with the changing landscape of Duchenne,” says Harvey. “There are over 30 clinical trials and over 40 companies working on Duchenne drug development. The improved standards of care are thankfully increasing the life expectancy of patients with this disease.”

But the availability of more trials means patients and their families face tough decisions when it comes to deciding which study they should pursue. Harvey explains her confusion in traversing the practical and emotional factors that contribute to the decision – something that other parents of children diagnosed with rare diseases must also face.

“What trial does my child qualify for?” Harvey asks when considering enrolling JB in a study. “What are the exclusion criteria? What is the goal of this treatment? Is a muscle biopsy necessary? Can my child do multiple MRIs? Can I afford the time off work to participate? How will this affect my family? Will he get the drug or placebo? And lastly, is this all worth it?”

The genetic basis of rare diseases like Duchenne only serve to complicate matters further. For example, while nearly all cases of DMD are caused by mutations in the *DMD* gene (which encodes the dystrophin protein) over 200 individual disease-causing mutations have been identified. This means that most disease-modifying treatments in development target only one, or a small subset, of the total number of known DMD mutations, limiting the number of patients eligible to participate in those drug studies.

“Many people do not realize that every child with a certain disease may not qualify for every trial,” says Harvey. “For instance, there are now drugs approved for Duchenne but they only help about 13 percent of patients. I cannot tell you how many emails and texts I get from people saying, ‘Did you hear about this? It’ll help JB, right?’ It’s hard to say, ‘yes, of course I heard about it, and no, it won’t help JB.’”

Of the trials JB was eligible for enrollment, Harvey says she relied on advice from physicians, clinical care centers, fellow parents and participation registries when making the difficult decision of whether or not to participate. But she stresses that patient wellbeing needs to be a priority when it comes to clinical trials, particularly when they involve children.

“I believe we need to have the child’s mental health at the forefront of our minds when we think about participation in clinical trials for rare diseases,” says Harvey. “That could include check-ins with social workers during visits, the inclusion of child life specialists to keep people entertained and happy.”

While it's still a challenge, Harvey has a positive outlook on the future of rare disease research.

"CROs and sites are talking about making trials easier," says Harvey. "I've been glad to hear that there is a shifting focus on the patient's quality of life. Overall, I feel like patients and their families are being heard. There's also the hard fact that if patients aren't in strong mental health, there will not be participants in the trials going forward. Clinical trials for many rare diseases, including Duchenne, will continue to increase and families are extremely grateful for all the work that is being done to get solid, scientific outcomes while considering the needs of the patients."

**Dr. John Lynn Jefferies, Michelle Petersen and Beth Woelfel Harvey discuss rare disease clinical trials and how patients can be the priority in this on-demand webinar.**