Overcoming Four Challenges to Successful Rare Disease Drug Development

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While it is difficult to develop drugs for any disease, rare diseases present additional challenges for designing and executing clinical trials. Overcoming the following four challenges can greatly improve chances for a successful rare or "orphan" drug trial.

1. Enrolling, Engaging and Retaining Patients

Challenge

By definition, rare diseases affect very few people. Also, rare disease patient populations are often widely dispersed and heterogeneous in disease subtype, symptoms, stages and exposure to prior treatment. Consequently, finding enough patients who fit inclusion and exclusion criteria for a particular trial can be difficult. Wide geographic dispersion may require developing research documents in several languages, which may complicate trial protocol development and administration, data collection, and outcomes measurement. Additionally, study sites in some countries may lack experienced study staff and diagnostic tools, requiring more administrative, training and clinical support.

Furthermore, three-quarters of rare diseases affect children, of which 30% will not live past their fifth birthday. Worldwide, these diseases are responsible for 35% of all deaths before age one. Trials in paediatric populations are therefore critical for rare disease research, yet introduce further challenges. It may be harder for children to communicate outcomes reliably, which may already be challenging due to multiple languages and differing cultural norms regarding reporting pain or other symptoms. Patients may also need significant financial or transportation support to participate in trials.

Solutions

Leveraging EHRs to improve patient recruitment:

Several approaches and tools can help sponsors identify and recruit patients, and develop workable trial designs and protocols. One involves using real-time patient data and physicians' notes from electronic health records (EHRs) to model various recruitment scenarios. This method identifies patients who match a trial's enrolment criteria and their proximity to prospective sites, and can even predict the incidence of qualified candidates among future patients, which helps identify promising sites and set realistic recruiting goals and timelines. The best way to access these EHRs is to partner with a CRO that already partners with organisations that collect EHRs.

ICON, for example, has access to millions of de-identified patient records through partnerships with IBM Watson and Explorys, as well as EHR4CR, a consortium that includes 11 sites in Europe. Also, ICON uses TriNetX, a research network and technology platform that connects the company to healthcare organisations that represent a further 57 million patients worldwide. ICON uses this data-driven approach to model protocol feasibility scenarios and advise clients on how many patients match trial criteria, where they are located and how they will recruit them.

Patient retention:

Retaining patients is critical in rare disease trials, where the loss of even a few patients may reduce data quality. Flexible approaches must be taken to minimise the burden to patients and their families. Prospective participants must be provided with practical support, and access to clear and comprehensive clinical information that enhances their understanding of the trial protocols. ICON's FIRECREST suite of digital products, for example, are designed to enhance patient recruitment and retention by using multimedia tools that help provide this essential support.

Patient engagement:

Clinical research site selection and support are also critical to engage patients and ensure protocol adherence. Sponsors can benefit from the expertise of global CROs who have experience dealing with sites that specialise in rare and orphan disease trials.

2. Designing and Evaluating Clinical Trials

Challenge

Four in five rare diseases are genetic and, therefore, chronic. Since many patients are severely ill, disabled, or must travel long distances, complex trial designs might be too burdensome. Trials must be simplified, flexible and attractive to enrol enough patients.

Identifying valid comparators within small patient populations is difficult. Standards of care often vary from region to region, so no uniform standard can serve as a comparator. In some cases, no effective treatments exist.

Designing a trial that can meet enrolment goals and designating an appropriate comparator make it difficult for orphan drug developers to gather sufficient data and build a compelling value story for their product.

Solutions

Simplicity is essential to designing a rare disease study that will attract patients. Patients may also find open-label or cross-over design trials more attractive than placebo-controlled randomised clinical trials (RCT). It is critical that clinicians, statisticians, and other well-qualified professionals collaborate to build a study design that is attractive to patients and develop a strong evidence-generation plan.

While identifying a valid comparator may be difficult, benchmarking treatment effects or demonstrating impact on patient health enables optimal evidence collection. Useful metrics include fewer interactions with the health system, improved patient health status, and the overall survival rate of individuals taking a new drug. Reimbursement chances can be enhanced by gathering these metrics during a clinical trial and comparing them with results from current healthcare practices. For instance, if an orphan drug leads to fewer transfusions in sickle cell anaemia patients, the health and economic benefits strengthen the reimbursement case.

Adaptive designs can be useful for rare disease trials by:

1) Preventing underpowered studies
2) Reducing patient recruitment needs through seamless multi-stage trials that protect patients
3) Enabling effective reallocation of resources through early termination

Tools such as ICON's ADDPLAN – a fully validated, regulatory compliant software platform that helps sponsors design, simulate, and analyse adaptive clinical studies – can ensure robust adaptive designs.

3. Ensuring the Quality of Patient Data

Challenge

Measuring clinical trial outcomes in rare disease patients is especially challenging because they often exhibit huge diversity in their clinical presentation and histories. Variables including age, disease progression, and disease severity influence reported outcomes, whether they are clinician-reported, observer-reported, or patient-reported outcomes (PROs).

Many rare diseases impact young children and cause disabilities. These patients often face challenges in self-assessment, especially reporting health status before and after diagnosis. One challenge is their tendency to accept their symptoms as a "new normal," diminishing their ability to accurately gauge their level of burden. Other patients may not be able to self-report after a time due to progression of their diseases. Heterogeneity among rare disease patients adds many complications to data collection and clinical outcome assessment (COA).

Solutions

Sponsors can benefit from engaging COA experts who understand the nuances of disease progression and PROs in rare diseases. They can provide tools and knowledge needed to support collection of valid data, and help find the most appropriate and valid PROs to include in their orphan drug development.

ICON's COA services are geared to the demands of global and national markets for patient-centred data. They can assist sponsors with: COA endpoints and trial design; assessment instrument selection, development, and validation; content validation; conceptual and endpoint model development; and regulatory support.

4. Navigating Global Regulatory Requirements and Gathering Payer Evidence

Challenge

Since rare disease research often does not fit the traditional RCT mould, collecting and communicating evidence that is compelling to regulators and convincing to payers is challenging. A firm understanding of how to navigate global regulatory environments is crucial to ensuring successful submission.

Because the definition of "orphan" changes from region to region, requirements for designation also vary. For example, rare diseases are defined as affecting less than 200,000 people, or about 6.5 per 10,000, in the US; fewer than five in 10,000 in the European Union; and affecting less than 50,000 people, or about four per 10,000, in Japan. Rare disease regulations also differ considerably by location.

On the payer side, insurers may require more evidence than regulators, including cost-benefit evidence for private payers in the USA and all payers everywhere else.

Solutions

Generating primary and secondary real-world data (RWD) that fulfils regional and worldwide regulatory and payer requirements is essential for rare disease drug success. Partnering with a CRO, such as ICON, which has a global reach, helps sponsors develop a deeper understanding of patient experiences and priorities, while accelerating market access for products that are aligned to payer and provider demands.

As international healthcare providers and regional regulatory bodies increasingly demand RWD, a patient-centric approach to collecting these data through wearables, apps, EHRs, and other sources will be crucial to contain costs and support payer negotiations. Furthermore, RWD can have tremendous value in early R&D decision-making.

In an advance ICON calls "Real World Intelligence," RWD is interpreted for clinical teams to align product development with specific unmet patient needs and hidden value opportunities. Sponsors can drive better site and patient engagement for more streamlined studies that meet payer and provider demands, and shorten the time-to-market.

Conclusion

Developing drugs for rare diseases involves complexities beyond those typically seen in large trials for more common conditions. Partnering with an experienced CRO gives access to expertise in trial design, execution and regulatory and payer filings that are essential for success.

ICON has conducted more than 200 rare disease studies involving approximately 25,000 patients at 6,420 sites worldwide. ICON has the experience and expertise you need to bring your rare disease drugs to market.