Overcoming Four Challenges to Successful Rare Disease Drug Development

W hile it is difficult to develop drugs for any disease, rare dis-
esases present additional challenges for designing and ex-
cuting 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 33% 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 phys-
icians’ 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 Explorx, 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 mil-
lion patients worldwide. ICON uses this data-driven approach to model feasibility scenarios and advise clients on how many patients match trial criteria, where they are loc-
cated and how they will recruit them.

Patient retention:

Retaining patients is critical in rare dis-
ease trials, where the loss of even a few patients may reduce data quality. Flex-
ible approaches must be taken to min-
-imise the burden to patients and their families. Prospective participants must be provided with practical support, and access to clear and comprehensive clin-
ic information that enhances their understanding of the trial protocols. ICON’s FIRSTREST suite of digital products, for example, are designed to enhance patient recruitment and re-
tention by using multimedia tools that help provide this essential support.

Patient engagement:

Clinical research site selection and support are also critical to engage pa-
tients and ensure protocol adherence. Sponsors can benefit from the expert-
ise of global CROs who have experi-
ence 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 pa-
tients are severely ill, disabled, or must travel long distances, complex trial de-
signs might be too burdensome. Trials must be simplified, flexible and attrac-
tive to enrol enough patients. Identifying valid comparators with-
in small patient populations is difficult.

Standards of care often vary from re-
gion to region, so no uniform standard can serve as a comparator. In some cas-
es, no effective treatments exist.

Designing a trial that can meet en-
rolment goals and designating an ap-
propriate 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 pa-
tients. Patients may also find open-la-
bel 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 compar-
or may be difficult, benchmarking treatment effects or demonstrating impact on patient health enables op-
timal evidence collection. Useful met-
rics 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 en-
hanced by gathering these metrics during a clinical trial and compar-
ing them with results from current healthcare practices. For instance, if an orphan drug leads to fewer trans-
fusions in sickle cell anaemia patients, the health and economic benefits strengthen the reimbursement case.

Adaptive designs can be use-
ful for rare disease trials by:

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

Tools such as ICON’s ADIPLAN – a fully validated, regulatory com-
pliant software platform that helps sponsors design, simulate, and an-
alyse 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 ex-
hibit huge diversity in their clinical presentation and histories. Varia-
bles including age, disease progres-
sion, and disease severity influence reported outcomes, whether they are clinician-reported, observer-re-
ported, or patient-reported out-
comes (PROs).

Many rare diseases impact young children and cause disabilities. These patients often face challenges in self-as-
essment, 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 accurate-
ly gauge their level of burden. Other pa-

tients may not be able to self-report after a time due to progression of their diseases. Heterogeneity among rare
disease patients adds many compli-
cations 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 pro-
vide 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 na-
tional markets for patient-centred data. They can assist sponsors with:

- COA endpoints and trial design: assessment instrument selection, development, and validation; con-
tent 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 evi-
dence that is compelling to regulators and convincing to payers is challeng-
ing. A firm understanding of how to navigate global regulatory environ-
ments is crucial to ensuring success-
ful submission.

Because the definition of “orphan” changes from region to region, re-
quirements 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; few-
er 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 regula-
tors, including cost-benefit evidence for private payers in the USA and all payers everywhere else.

Solutions

Generating primary and second-
ary real-world data (RWD) that fulfills regional and worldwide regu-
larity and payer requirements is essential for rare disease drug suc-
cess. Partnering with a CRO, such as ICON, which has a global reach, helps sponsors develop a deeper understanding of patient experi-
ences and priorities, while accel-
erating market access for products that are aligned to payer and pro-
vider demands.

As international healthcare providers and regional regulatory bodies increasingly demand RWD, a pa-

tient-centric approach to collecting these data through wearables, apps, EHRs, and other sources will be cru-

cial to contain costs and support pay-
er negotiations. Furthermore, RWD can have tremendous value in early R&D decision-making.

In an advance ICON calls “Real World Intelligence,” RWD is inter-
preted for clinical teams to align prod-
uct development with specific unmet patient needs and hidden value op-
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 ap-
proximately 25,000 patients at 6,420 sites worldwide. ICON has the experi-
ence and expertise you need to bring your rare disease drugs to market.