How Engaging Patients in Trial Design Maximises Orphan Drug Success

PEER REVIEWED

Orphan drug discovery is characterised both by extraordinary opportunities and challenges. The potential to affect the course of medicine is every bit as significant as the promise of changing the lives of people who suffer from lifelong, debilitating conditions.

Yet, research in this space is also associated with some of the highest hurdles in medicine. Orphan drugs, by their very nature, treat small, complex patient populations. Thus, clinical trial design and execution require a level of scientific expertise, operational acumen, regulatory knowledge, and patient engagement skills that many sponsors find daunting. Indeed, algorithms have been created just to assist in the selection of appropriate alternate trial design, given the emphasis placed upon maximising patient exposure and reducing the overall timeline for development prior to market authorisation or NDA submission.[1]

Fortunately, regulatory flexibility and financial incentives can help build a strong business case for conducting orphan drug trials, in the context of exceptionally innovative clinical development programmes. Amid a scarcity of research resources, the US Food and Drug Administration (FDA), European Medicines Agency (EMA), and others apply special considerations to rare disease trials. Notably, a study published by the National Organization for Rare Diseases affirms the effectiveness of programmes like the Orphan Drug Act of 1983 and reinforces the need for continued flexibility, which has been demonstrated from the FDA.[2,3]

Backed by a friendly financial and regulatory framework, sponsors can participate in orphan drug research with greater confidence. The key to a successful outcome, however, is to engage patients and advocacy groups at a deeper, more personal level. Even the language typically used must change: It is not enough to "recruit" or "retain" patients for an orphan drug trial, we must "engage" them in the process of programme design and the articulation of benefits and risks. A successful orphan drug programme is all about understanding not only the clinical disease at hand but also how patients and their families experience the illness in their daily lives.

Orphan Drug Discovery: Recognise the Inherent Nuances and Challenges

The journey for a patient with an orphan disease is often marred with frustrations and setbacks. It's not uncommon for patients to spend years seeing multiple specialists before they even receive a diagnosis. Once a rare disease is identified, a patient's entire life may revolve around trying to find a cure, all while managing any functional limitations that may accrue.

Small patient populations coupled with significant clinical heterogeneity and complex lifestyles and disease dynamics make patient engagement particularly challenging. That's why it's vital that sponsors first understand their patient population – how they live and the far-reaching impact of their illness on both the individual and family – in order to create an informed research and clinical development programme.

The second step is to design a trial that reflects the knowledge of what patients and families are up against, i.e., a protocol structure based upon visit frequency or visit density (the number of assessments/visits) and the need for specialised testing, which is consistent with ongoing standards of care. Protocols must account for highly diverse clinical manifestations and disease progression, as well as accommodate patients and families who live complicated, demanding lives.

This factor alone requires a level of finesse and expertise not typically found in clinical trials for more common conditions, with more traditional development programmes. It also requires a higher level of collaboration and engagement with families and advocacy groups at an earlier phase of research. It's important not to overlook that patients with rare diseases are often part of close-knit communities. Both positive and negative information about a product's attributes or an ongoing clinical trial can spread rapidly across these patient populations, and sponsors who hope to engage the right participants must develop a level of trust that results in widespread endorsement with information that is both timely and accurate.

Elements of a Patient-Centric Trial Design

Because the success of orphan drug research is intrinsically connected to the right participant engagement strategies, sponsors should prioritise a patient-centric trial design that considers the following elements:

- **Collaboration with advocacy groups**
  More than 7000 rare diseases exist, which makes it nearly impossible for sponsors or contract research organisations (CROs) to be experts on all of them. Indeed, the most laudable skills are those that are fungible across diverse indications, which permits adaptation to one indication based upon the experience of evaluating another. That's why collaboration with advocacy groups from the outset – even before protocol design – is imperative to understanding the patient journey connected to a particular illness and identifying appropriate end points. In fact, without buy-in from these groups, it's very hard to conduct a successful orphan drug trial as either the design or other pragmatic constraints of study enrolment limit patient participation.

  Keep in mind, however, that not all advocacy groups will be quick to endorse a trial, and their purpose may differ markedly as a reflection of their primary focus. When there are numerous groups to choose from representing a particular orphan disease, sponsors and CROs must determine the main players and then build genuine relationships that can help establish trust across the continuum of development.

- **Branding that captures the patients' voice**
  Once partnered with the right organisations, sponsors and CROs can collaboratively brand a study in a way that reflects the patients' voice. Patients and families are much more likely to respond positively when all education and communication is consistent and familiar and when they feel like their experience and input matter.

- **Support for patients**
  Daily life for patients with rare diseases may be very draining, with multiple comorbidities, and families are often overwhelmed with the tasks involved in managing the illness within the framework of regular life responsibilities. Sponsors who implement support services are much more likely to engage patients and families for the long term. Some of these services may include:

  - **Transportation and travel.** These are huge factors for many patients. Limited patient numbers often necessitate a global approach to orphan drug research, and patients may be spread across large geographical territories. In one study involving a rare metabolic disturbance, for example, a patient flew across 11 time zones every two weeks. Without assistance from the sponsor and the supporting CRO, the travel challenge likely would have meant the patient could not participate. This one example also emphasises the importance of linking experimental design with the pragmatism associated with clinical operations because they are intrinsically the same consideration.

  - **Visit frequency and density.** Establishing home nursing visits can ease travel burdens by decreasing the number of site visits required, especially if the study requires many site visits or the patient has compromised mobility. Many assessments can be done in the patient's home by skilled and protocol-trained nurses. These assessments can include abbreviated physical examination, adverse event and concomitant medication recording, CSSRS questionnaire, abbreviated neurology examination, ECG recording, blood draw, IMP compliance, multiple quality-of-life and neurological function assessments, and more. When patients do travel, it's imperative to make maximum use of site time by scheduling as many specialist meetings as possible at each visit without overwhelming the patient. Indeed, recent trends within the industry showcase the potential value of "at home" versus "within clinic" as sessments, with responsibilities parsed based upon the competency of home versus clinic personnel.[4]

  - **Sibling and pet care.** The impact of disease burden and study burden on the entire family must be considered. Ensuring care for siblings or pets during a trial may make it possible for families to participate and to do so relatively unencumbered regarding concerns about family members.

  - **Ongoing communication.** Keeping patients and families educated and engaged requires ongoing communication, both to build interest and to ensure all their needs are met. Online portals offer an effective means for easing and centralising communication. In addition, regular communication through email or text can enhance satisfaction by reminding patients about appointments, what they need to bring, or just simply what to expect. Managing the communication process is critically important during studies conducted under GCP (Good Clinical Practice), given the oversight mandated for study participants.

- **Support for clinical sites**
  An online portal to help support each site – complete with training, study protocols, education resources and contact points – is a critical part of this equation, as well. Branded materials, pocket protocols, lunch-and-learn materials, referral letters, and other resources can ease the participation burden for sites.

Capture All the Benefits of Orphan Trials

In the US and elsewhere, administrative flexibilities that reduce timelines and costs for orphan drug studies can lower the development risk for sponsors. Tax credits and other financial incentives enhance the attractiveness.[5] Consider, for example, that simply acquiring an orphan designation can increase a public company's valuation by 3-10 per cent, contingent upon the size of the organisation, in the portfolio on the development.[6]

Partnering with a CRO experienced in innovative approaches to orphan drug trials can help sponsors achieve timely, effective results. The innovation extends from methods of regulatory interface, the innovative portfolio of experimental designs that could be considered, the operational acumen that must be specifically tailored toward project execution, and the overarching need to embed patient-centricity into a formal clinical development process. When a patient-centric trial design complements an already attractive regulatory outlook, opportunity abounds. Rare disease research presents a strong business case for advancing medical practice and improving the lives of some of healthcare's most disadvantaged patients by maximally exploiting advances in research and development and in clinical trial methodology. It's an important mission for healthcare, and one that is ripe for future expansion.

REFERENCE

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