Overcoming Challenges in Orphan Drug Development

While there is no 'out-of-the-box' roadmap for orphan drug development, through a toolkit of innovative solutions, we can address the unique aspects of clinical development in rare diseases, upfront

Rachel Smith at Veristat

Developing a product to treat orphan disease presents both opportunities and challenges. Unlike a traditional small molecule in a non-rare disease, the roadmap from bench to market can be poorly defined and the unique aspects of ultra-rare diseases can present significant hurdles during clinical development. While regulatory agencies offer incentives for orphan drug development, such as access to protocol assistance, grants, reduced fees, expedited marketing application reviews, and even market exclusivity; the cost of developing these products remains high. For orphan drug development to be commercially viable, it is integral that regulatory and clinical strategies are designed to address potential challenges upfront. Key obstacles include understanding the disease, access to a sufficiently large patient population, and patient engagement.

Eligibility and Endpoints

By the very nature of these ultra-rare diseases, we are looking at low patient numbers, with the EMA defining orphan as a disease affecting no more than 5 in 10,000 people and the FDA defining this as affecting less than 200,000 people. Data pertaining to diagnosis, clinical management, and disease progression in most orphan conditions is, therefore, extremely limited. In addition, management of these diseases can vary significantly across countries with a lack of consensus on clinical endpoints, especially as the patient population is rarely homogenous, disease severity is often variable, and the comorbidity burden is often high.

Obtaining natural history data is crucial in rare disease product development where national or international disease registries are not in place, as this is an opportunity to collect a consistent dataset in the target condition, allowing identification of current standard-of-care processes, homogenous sub-populations, and trending typical disease progression. These data are valuable, not only in informing protocol design, but can be used as a comparator dataset as the product moves towards commercialisation. The scope of natural history trials can be extended to enable validation of intended protocol endpoints, including biomarkers and clinician or patient reported outcomes (PROs) where validated endpoints do not exist. Natural history trials also offer opportunities to initiate relationships with key opinion leaders (KOLs) and clinical sites with expertise in the target disease and access to adequate patient numbers, to support progression from bench to early phase clinical trials.

Due to the value of these trials, early implementation is recommended before the product itself moves into clinical trials, engaging a biostatistics team with extensive experience in ultra-rare diseases and knowledge of regulatory requirements to support sample size estimations, endpoint identification/validation, and protocol design for an orphan designation.

It is particularly important for early-phase trials aimed at establishing initial safety and efficacy to ensure the patient population is as homogenous as possible with a low comorbidity burden to obtain clear trial outcomes. With such small patient populations, identifying the ideal patient pool is an added challenge, and only possible in consultation with KOLs in order to strike the balance between a 'pure' population and achievable enrolment figures. While early phase trials should be designed with relatively restrictive eligibility criteria, it is recommended to include a broader population in later phase trials to prevent limiting the product label at the point of commercialisation. Adaptive trial design, or inclusion of multiple arms representing sub-populations, are successful solutions to achieve this.

	Pros	Cons
Retrospective Studies In retrospective studies, the patient evaluations have already occurred, and data is drawn from existing medical records compiled for patient care.	May be performed more quickly than prospective studies, since the data are already available. Can collect and organise important information about a disease and identify gaps to be addressed in prospective data collection and analysis. Adjudication committees are key to reducing bias.	May be limited by such factors as incomplete data, variability, and inconsistency in collection, length-biased sampling, and other potential selection bias.
Prospective Studies In prospective studies, new evaluations are conducted according to a prespecified data collection plan that may reflect current data standards.	Can address many of the limitations encountered in the retrospective approach (e.g., by following standard operating procedures and a consistent patient examination schedule).	Generally require more time than retrospective studies, depending on needed duration of observation – particularly for longitudinal studies.
Cross-Sectional Studies In cross-sectional studies, data are collected from across a cohort of patients during a specified, limited time period. May be either retrospective or prospective.	Can be of value in drug development for a rare disease because they can indicate the general course of the disease through various stages.	The data may not fully characterise the disease course and identify subtypes that may be less well characterised because of length-biased sampling.
Longitudinal Studies In longitudinal studies, data are collected from patients at several points over time. May be either retrospective or prospective.	Typically yield more comprehensive information about disease onset and progression over time than cross-sectional studies, so they tend to be more useful as a source of natural history information.	Generally require more time to conduct than cross-sectional studies, and are more resource intensive.

Figure 1: The benefits and drawbacks of natural history studies

To Blind or Not to Blind?

The gold standard clinical trial design is a double-blind, randomised, placebo-controlled trial. With rare diseases, we are seeing a movement towards novel products where the gold standard design is not possible, either due to ethical considerations or lack of viability with low patient numbers, for example, gene therapy. This means we are having to come up with more creative solutions, bespoke for the target disease and product type.

The use of synthetic control arms using real-world data is one of the solutions to demonstrate to regulators that these novel products are safe and effective when compared to untreated patients. Synthetic control data can come from multiple sources: disease registries, natural history trials, electronic health records, or historical clinical trials, to name a few. Synthetic control arms also pose a potential solution to heterogenous patient populations, allowing patient-pairing between treatment and control arms, or even using the patients themselves as a control, based on their historical pre-treatment medical records or participation in a natural history trial.

Where the gold standard double-blind design is viable, special considerations should be taken on how the double-blind is maintained, in the most robust and ethical manner. With a large number of novel products in development, product

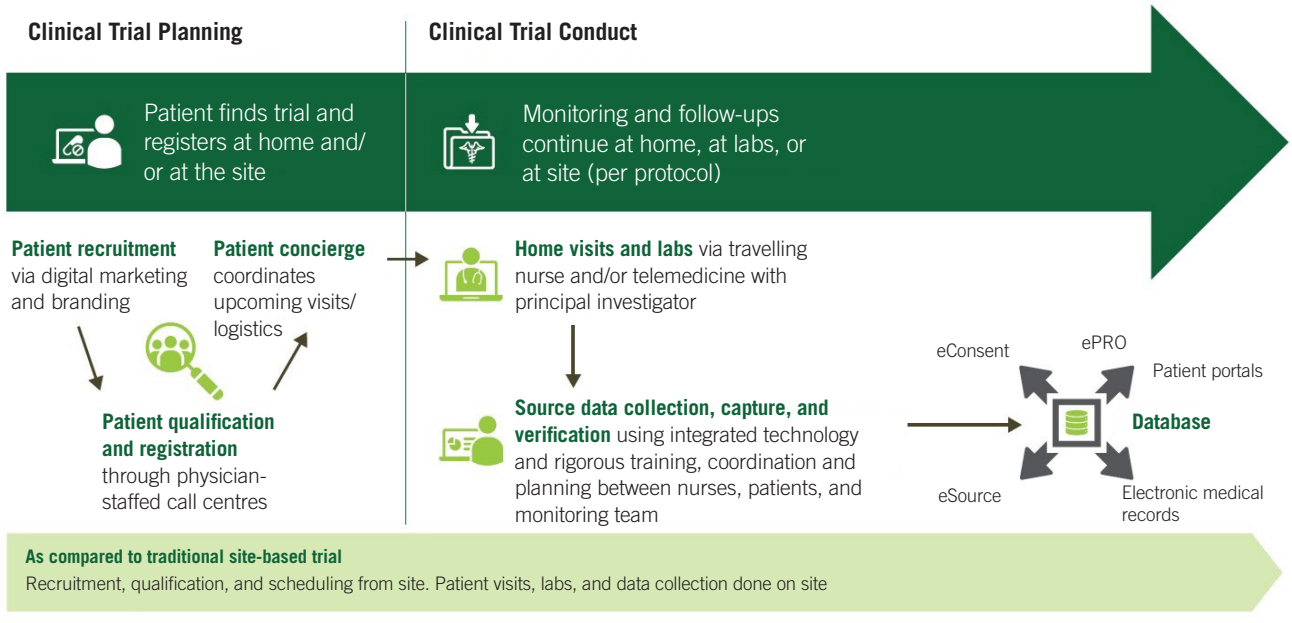


Figure 2: The patient's journey through the virtual clinical trial experience

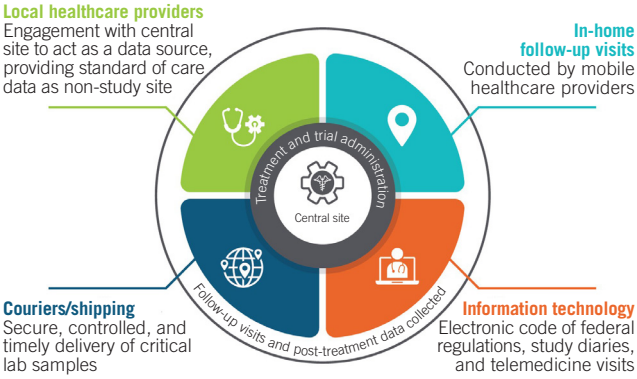


Figure 3: Central site model

administration is rarely as simple as taking an active or placebo tablet. Administration procedures can be invasive, such as neurosurgical or intrathecal administration, and require the introduction of sham procedures, which mimic aspects of the procedure as performed by an unblinded surgical team, to maintain the blind for the patient and clinical teams while upholding high ethical standards.

Patients, Patients, Patients!

Our top priority in drug development is the patients. This is amplified in orphan diseases where treatment options are limited and rarely curative, often treating symptoms with variable success. For this reason, it is essential to put the patients at the heart of everything we do, with regulator's expectations shifting towards patient-centric approaches.

Many advocacy groups, and even national organisations, such as the National Institute for Health Research, have developed infrastructure for companies to engage with patients directly to encourage patient involvement and focus trial design around the participant journey. Patient feedback on visit schedules, assessment burden, travel logistics, and blinding/sham procedures has demonstrated positive recruitment and retention numbers. In some cases, feedback has allowed the inclusion of additional endpoints as participants and their families are living with the disease day-to-day, so are best placed to determine what a meaningful improvement in their disease symptoms or quality of life would look like – this could be as simple as being able to pick up a piece of cutlery to eat their own meal.

With patients in mind, developing patient-centric virtual clinical trial design has been key to clinical trial success in orphan disease as this reduces the patient travel burden by delivering the trial directly to them. Traditionally, patients have been required to travel to a clinical site for all visits. However, with fully virtual or decentralised trials all visits are performed via telemedicine or in the patient's own home with direct-to-patient drug shipments, at-home laboratory sample collection and at-home nursing. Advances in technological solutions for eConsent, eSource, ePRO, and logistical support have enabled virtual clinical trials to become a reality.

The Full Experience With a Hybrid Decentralised Trial Model

Fully virtual or decentralised trials are not a suitable option for every trial, depending on the target disease or investigational product type. For example, autologous gene therapies require on-site visits for cell collection, conditioning, and product administration procedures. However, during initial screening or following product administration, visits do not necessarily need to be performed at the trial sites and can be managed via a central site model. As the name indicates, a central site model allows patients to be treated at one or two central sites. A combination of technology and/or mobile staff are employed to conduct follow-up visits in a convenient, local setting or at the patient's home. This model has been used to successfully enrol out-of-country or out-of-state patients at a central site, essentially offering a global population. If correctly set up, the central site model offers a more cost-effective and efficient solution than the opening of tens of trial sites across multiple countries while accessing a broader net for patient recruitment and reducing the burden of trial participation on patients and their caregivers.

Central Site Model Explained

Offering clinical trials with low travel burden and providing white-glove concierge services for door-to-door transport where travel is unavoidable are proven to increase patient recruitment and retention, particularly in ultra-rare diseases where routine clinical care is often burdensome, and the risks of frequent travel can be too high.

Challenges of Orphan Drug Development – Solved?

There is no 'out-of-the-box' roadmap for orphan drug development. Too many variables exist to allow for a 'cut-and-paste' approach. Even as we gain more orphan drug designations and approvals, it is unlikely that we will ever reach a point of 'one size fits all'. However, we have developed a toolkit of innovative solutions to address the unique aspects of clinical development in rare diseases upfront, enabling a tailored strategy for success by designing the clinical programme based on robust disease data, and putting the patient front-and-centre of trial designs.

Rachel Smith, Portfolio Director at **Veristat**, has worked in clinical research for over 10 years across all clinical phases (I-IV) with a focus on complex advanced therapy trials in rare disease. Rachel is currently the Portfolio Director of global cell and gene therapy programmes, and the lead for the Veristat Global Cell and Gene Center of Excellence. Rachel has a BSc (First Class Hons) Biochemistry from the University of Warwick, UK, and is a Registered Member of the Institute of Clinical Research.

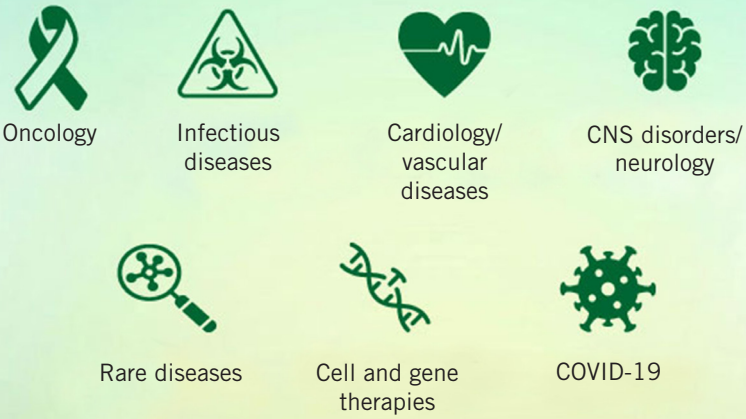
Scientific Expertise to Solve Any Clinical Development Challenge

With more than 26 years' experience in clinical trial planning and execution, Veristat is equipped to support any development programme

Getting a novel therapy through the clinical development process to approval is complicated, full of challenges, and even more complex in the current COVID-19 world. Veristat has assembled an extraordinary team of scientific-minded experts who strategically design and execute clinical trials and prepare your clinical data for regulatory review. Our integrated regulatory, clinical, biometrics, safety, and medical writing experts support small to mid-sized biopharmaceutical companies running their development programmes throughout Europe, North America, and many other regions worldwide.

Our team has prepared over 100 marketing applications for approval with global regulatory authorities in the last 10 years.

Therapy centres of excellence

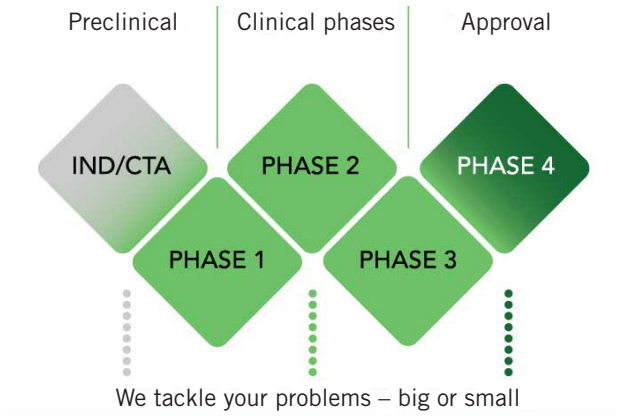


Complexity Is Our Specialty

Veristat's focus on novel drug development has led to success when handling the unknowns that arise across complicated therapeutic areas, such as rare/ultra-rare disease, advanced therapies, oncology, and infectious disease trials. We apply this knowledge base every day to solve any clinical programme's challenges, from the simplest to the most complex.

Helping you make and implement the right decisions at the right time is our strength. Let us help you overcome your challenges and advance your compound to the next step in the clinical development process.

Mitigating risks along the entire clinical development and regulatory approval lifecycle



Avoid Unknowns from the Start

We are here to establish patient safety throughout clinical trial planning and conduct, navigating the regulatory approval process, and post-marketing surveillance. When you start thinking about your first-in-human trials or how to solve all the complex challenges, it is time to contact us. Veristat has the right resources to help you navigate:

- Clinical trial planning
- Clinical trial conduct
- Marketing application process and post-market pharmacovigilance

VERISTAT

Veristat Corporate Headquarters
134 Turnpike Road, Suite 200
Southborough, MA 01772 US
veristat.com
insights@veristat.com
UK | Spain | Taiwan | Canada | US