Essential investments in optimising clinical research for rare diseases

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Abstract

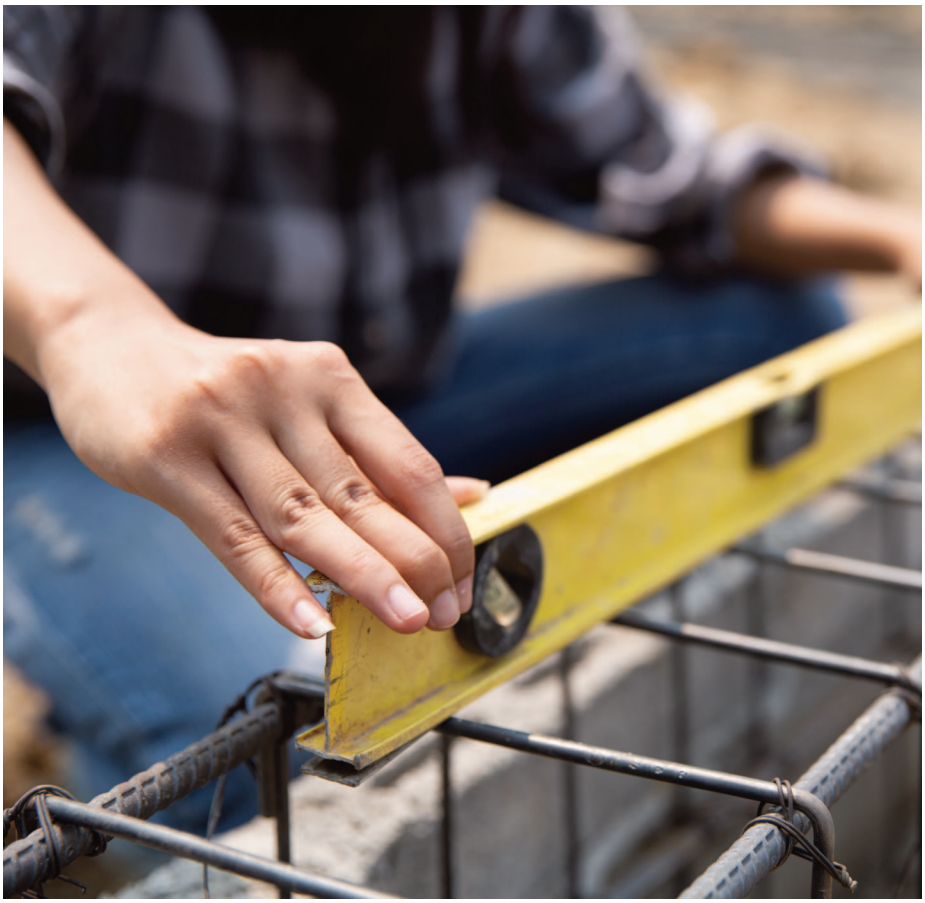
The complexities associated with clinical trials for (ultra) rare diseases include regulatory and logistical hurdles and the challenge of building trusting relationships with health authorities, patients, and clinicians. Significant obstacles include the identification of relevant endpoints, sample size limitations, and the cost of maintaining diverse clinical sites. Recruitment and retention of study participants are complicated by site inexperience and the specialised nature of rare disease management, necessitating comprehensive training of site staff and effective communication strategies. All these hurdles directly or indirectly impact the regulatory medical writer preparing complex rare disease clinical documents that comply with regulatory and industry standards.

Introduction

The definition of *rare disease* varies between countries or territories, being a disease or condition affecting fewer than 200,000 patients in the US or with a prevalence of ≤5 per 10,000 inhabitants in the EU.[1] *Ultra-rare* diseases are defined as rare diseases that have a prevalence of <1 per 50,000 persons.[2,3] The field of clinical research for rare diseases presents distinct challenges that significantly influence study design, execution, and outcomes.[4–7] The limited research available for rare conditions complicates the identification of relevant literature and the development of robust clinical protocols. Furthermore, developing positive relationships with patients and clinicians is a vital part of executing a rare disease clinical trial. Here, we discuss the complexities of conducting clinical trials for (ultra) rare diseases, with particular focus on regulatory and logistical hurdles, and on the importance of building collaborative and trusting relationships. The success of such trials requires significant upfront investment of time (and money) building solid foundations with regulatory authorities, patient groups, key opinion leaders, and clinical sites, to shape an executable protocol. Regulatory medical writers play a key role in preparing this protocol and other complex rare disease clinical documents that comply with regulatory and industry standards. In an area where experience is limited, every participating person or organisation is a trailblazer in their field and any process or system is deployed in an unfamiliar manner.

Protocol and study design

Given the complexities of rare diseases, where conventional research frameworks may not be directly applicable, it is crucial to invest adequate time upfront to develop a well-designed, executable protocol in collaboration with experts. This will ultimately save time, cost, and frustration. Rushing the process increases the regulatory medical writer's burden because of the need for multiple protocol amendments, which likely result in delayed study timelines as well as increased costs.



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Critical factors that must be addressed when designing trials for rare diseases include:

- **Primary and secondary endpoints:** Identifying appropriate primary and secondary endpoints is complex because of limited existing data. The rarity of the disease may require novel or adapted endpoints (including patient reported outcomes) to accurately assess treatment efficacy and safety. In the absence of relevant endpoints, surrogate endpoints or biomarkers may be considered when agreed by the health authority. Involving a rare disease patient advocacy group (when available) may prove valuable in determining relevant and nuanced endpoints[8] as rigid interpretation of predetermined endpoints may result in an unfair *study failure* of an effective treatment.
- **Sample size and data points:** Achieving an adequate sample size is challenging because of the scarcity of eligible participants. A careful balance should be considered between sampling frequency and the burden on the patient and study personnel. A small sample size can undermine the statistical power of the study, complicating the determination of significant outcomes,[9] while intensive sample collections for sufficient data points may discourage both patients and investigators. Statistical methodology is critical to handle missing data, patients lost to follow-up, and interpretation of outcomes with small sample size.
- **Control arm and dosing:** Determining an appropriate control arm and dosing regimen is another difficult area. Given the rarity of the condition, standard control groups[10] may be unavailable, and dosing strategies must be tailored based on limited pre-existing data.

The US Orphan Drug Act of 1983 and similar legislation in the EU encourage companies to develop drugs for rare diseases. Drugs are granted an orphan designation if they are for the treatment of rare diseases that are life-threatening or seriously debilitating.[1] Securing orphan designation for a drug can provide advantages such as access to protocol assistance from regulatory authorities.[11,12] Unlike common conditions, rare diseases often require numerous and iterative communication with health authorities, thus falling under this assistance procedure. The lack of established precedents can increase the likelihood of disagreements and delays, as both the applicant and the regulatory body must navigate uncharted territory. Therefore, investing early in relationships with health authorities and incorporating their input on protocol design and endpoint agreements, along with contributions from patient advocacy groups, key opinion leaders, and clinical sites, will lead to improved study design.

> Traditional clinical trial management systems are not optimised for rare disease studies, and key performance indicators are not applicable because of the low participant numbers.

Inclusion and funding of clinical sites

Collaborating with clinical sites at the time of protocol development will help ensure that the protocol is executable and reduce the need for protocol amendments at a later stage. However, while inclusion of clinical sites at an early stage is of great benefit, for rare disease trials this is complex and far more costly than for standard trials. Qualification criteria for clinical sites to run rare disease trials are unclear or complex, patient pathways may be unknown, and networks for referrals may not be set up. Prevalence or incidence data regarding a condition are very limited and often reflect regional epidemiological data only; this complicates assessing which countries should be in scope for the trial. Clinical trial naïve sites often need to be included for rare disease studies, adding to the complexity both in defining the site selection criteria as well as in the conduct and execution of the trial. However, given the low probability of identifying eligible participants, qualification of a sufficient number of sites is crucial. Funding considerations include supporting single sites across multiple countries rather than consolidating sites within one or two countries and maintaining these international study sites even when participant recruitment is minimal. In addition, the international regulatory approval system is complex; this may cause lengthy delays for clinical trial set-up.[13] Sites recruiting no or only a few patients annually require high maintenance and bespoke communication, as risk-based monitoring is insufficient because of low enrolment numbers. Traditional clinical trial management systems are not optimised for rare disease studies, and key performance indicators are not applicable because of the low participant numbers. In addition, the often-inexperienced site personnel must undergo extensive training (further discussed below) and attend investigator meetings for potentially enrolling only one participant, if any.

> Given the small number of eligible participants, all sites that are willing to recruit are indispensable and investment in optimising coordination, communication, and the relationship with the site in general is crucial.

Recruitment and site support

Screening, recruiting, enrolling, and retaining participants in rare disease clinical trials present unique challenges. Practical aspects of recruitment and retention in clinical trials of rare diseases were previously discussed by DeWard et al.[14] Here, we add our experiences to the authors' collective experience.

Naïve sites

Clinical sites selected for (ultra) rare disease trials may be inexperienced with running clinical trials in general or with rare disease trials specifically. Therefore, the investment in education of clinical site personnel, regarding clinical trial processes, systems, and disease awareness for potential referral sites, should not be underestimated. The site may not have a study coordinator if there was never a need for such a role before, and contracting may be outsourced given that hospitals are often very large organisations. The local investigator might be unaware of how to conduct internal follow-ups and likely has a full-time role without a structured framework for clinical trials. Therefore, any email, phone call, or request from the sponsor could feel like an additional burden while many of the activities required for trial success may need to be highlighted on a regular basis. Coordination by a single point of contact at the sponsor to a specifically appointed coordinator at the clinical site may help the investigator navigate both new worlds: of clinical trials and of the rare condition. This involves clarifying acronyms for roles and

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processes that may be unfamiliar to site personnel and ensuring that the site comprehends the study processes both within their own organisation and in relation to the sponsor. Personnel may have been trained months or even a year before their first patient is enrolled; continued site engagement and support during the period between start-up and first participant enrolment may avoid the need for re-training. Once a patient has been identified, it is important to ensure that site support is available throughout the entire clinical trial journey for that patient. Establishing relationships based on trust and collaboration with open communication between the study sites and sponsor may help to prevent issues such as: following standard care protocols where these are not appropriate, missing timepoints in irregular study follow-up schedules, and reporting normal ranges of laboratory values where these are not applicable. In short, lack of experience can result in deviations from required study processes and inappropriate reporting. Therefore, it is essential to slow down and explain things gradually and comprehensively, without presuming any prior experience from the clinical staff or their organisation. This can help ensure the site is set up for success when they do identify a suitable participant. Furthermore, facilitating connections between participating sites is critical for trial success, for enquiries or support, and to aid information sharing and lessons learnt related to best practices, challenges and successes.

The integrity of rare and valuable study samples (further discussed below) may be at considerable risk at inexperienced sites. No experience with specific analyses requires shipping from a clinical site to the laboratory where the applicable assays are available. No experience with sample handling may result in shipping delays resulting in sample loss or samples that cannot be analysed. Training of local site personnel may be considered for sample analysis; however, this may not always be possible because of the specific infrastructure, facilities, and expertise required for sample handling and analysis. Local analysis at multiple sites may also result in unwanted inter-assay variation, which will have a considerable impact on the results, considering the small sample size. Investment for the highest anticipated benefit should be considered: use an established central laboratory, involving shipping risks and possibly high maintenance costs, or use local laboratory analyses, which may be more costly and result in inter-assay variation.

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Expert sites

Sites with specialised knowledge may face challenges if overwhelmed by multiple requests. It is key to understand the position of the site to ensure interactions do not become a burden or irritation. Here too, established coordination through a dedicated point of contact at the sponsor to a specifically appointed coordinator at the clinical site can facilitate task prioritisation, reduce the burden on the local investigator, and prevent frustration. This sponsor contact may also share expert learnings with the other participating sites. Given the small number of eligible participants, all sites that are willing to recruit are indispensable and investment in optimising coordination, communication, and the relationship with the site in general is crucial.

Eligible participants and study burden

Another challenge to screening and enrolling eligible patients is the correct diagnosis of the rare condition. A condition may be so hard to identify that patients often have consulted several different specialists over many years before they are accurately diagnosed. In contrast, recruitment of pregnant individuals whose foetus has a rare condition is only feasible within a limited time frame during the early phase of the pregnancy.

Minimising blood sampling in very young children while maximising data collection from the limited number of participants should be considered to minimise participant study burden. Numerous exploratory endpoints may increase any participant burden because of increased blood sampling, more or longer visits, or additional questionnaires. Other study-related requirements may also be perceived as a burden, such as the number or type of treatments or injections, or having to alter medication that patients are already taking. There is a need to carefully consider what is important to prevent the protocol from being overburdensome. Participants may drop out of a study if the burden is perceived as too high, thereby reducing the already minimal analysis set. Given the (ultra) rare condition, it will likely prove impossible to recruit additional eligible participants. This underlines the value of each single obtained study sample, and therefore the importance of positive participant experiences for optimal retention. Swift stipend timing should not be underestimated as part of this positive experience. Effective communication between the participant's primary care

team and the study team is also essential to ensure their care team is provided with the study information and understands what the participant has already been through.

Considerations for the regulatory medical writer

All hurdles discussed above directly or indirectly impact the regulatory medical writer. As best practices may not be available or will evolve during the trial, study design decisions or strategy positions or both may not be clear or confirmed prior to the start of writing protocols, protocol amendments, or health authority communications. Both the lack of background information on the (ultra) rare disease and the lack of rare disease guidance with TransCelerate[15] template(s) can be a challenge with all clinical document types. The regulatory medical writer will likely encounter many more rounds of review and revisions than usual, because of continuously advancing insights regarding best practices for the specific rare condition. Close collaboration with the study team is essential, anticipating continuous study and document adjustments and preparing for health authority interactions at all stages of the study and document submission.

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Protocol amendments

The pioneering nature of rare disease trials often leads to frequent protocol amendments, both before and during the trial. Common areas for adjustment include:

- **Inclusion and exclusion criteria:** With improved diagnostic methods, laboratory assessments or disease management guidelines, modifications may be necessary to better align with the actual patient population.
- **Study design and recruitment:** Changes to study design or participant numbers may be needed if initial recruitment targets are unmet. A redesign may accommodate the available participant pool or real-world data may be considered, complementing the prospectively collected clinical data, for meeting the required sample size and acceptable statistical interpretation.
- **Study sites:** New sites may be added, or existing sites closed, throughout the trial's duration.

Study reports

Writing the clinical study report for rare diseases can be challenging because of exceptions such as study procedure deviations, incomplete data sets, and adjusted analysis methods. Incomplete data sets due to participant dropout or discontinuation of investigational treatment may be a significant part of the analysis. Descriptive decision rules may be employed to draw conclusions from available data when statistical significance is difficult to achieve. Lean report writing and maintaining anonymity are difficult as clinical teams are more inclined to provide in-text narrative descriptions for each individual participant because of the small sample size. This feature of a rare disease clinical study is not covered in reporting guidelines, making it difficult to reach cross-functional agreement on a common reporting approach. Note that for both the patient narratives and for the lay summary, maintaining anonymity is exceptionally important, given the small number of trial participants.

Conclusion

Conducting clinical trials in rare diseases demands a nuanced approach that addresses the unique challenges of limited research, regulatory interactions, inexperienced clinical sites, and participant recruitment. Ensuring adequate time is allowed upfront to develop a solid foundation will enhance the likelihood of a well-designed, executable protocol. For rare disease trials, both the pace and way of working need to be adjusted. By understanding these dynamics, investment in positive relationships with authorities, clinicians and patients, and preparing for potential protocol amendments, researchers can better navigate the complexities of rare disease trials. Strategic planning and flexibility are key to regulatory document development and advancing treatments to improve outcomes for patients with rare conditions.

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Disclosures and conflicts of interest

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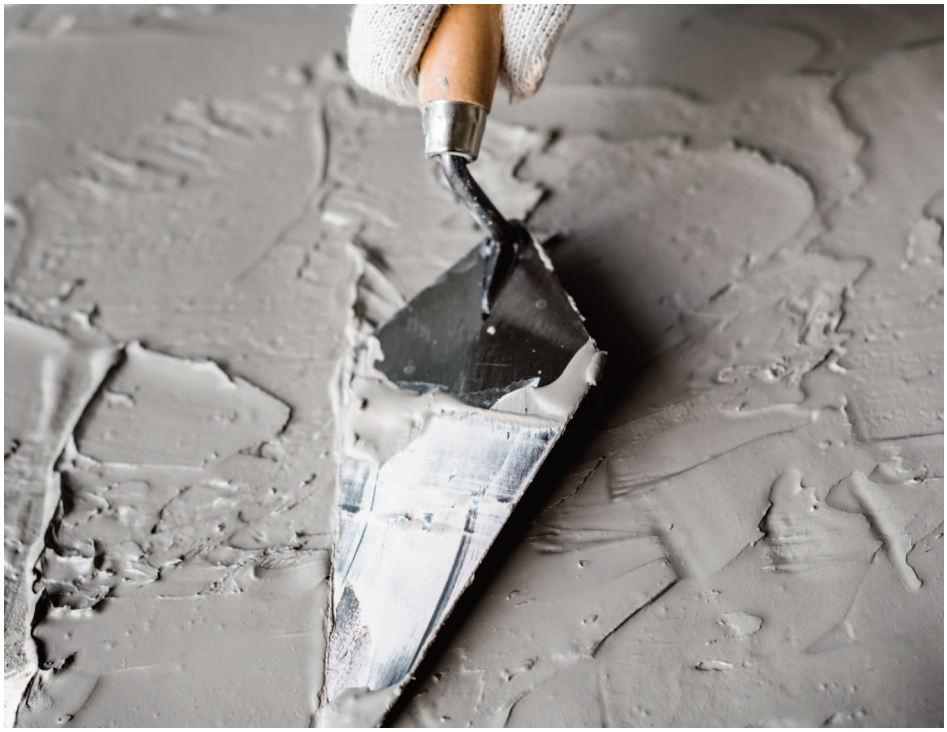

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