Clinical Trials in Rare Diseases: Every Patient Counts
Identifying sites and optimizing patient recruitment and retention in rare disease studies

ABSTRACT
In many rare and ultra-rare disease studies, sponsors do not have the luxury of choosing the countries or sites where the study will be conducted. Instead, they must use the sites where those patients are already being treated, regardless of geography. Additional protocol criteria – such as treatment-naïve patients or general prevalence of a disease by region – may limit site selection even further, requiring the sponsor to open sites in countries that normally would not be considered for clinical trials.

In this white paper, we explore the many aspects of clinical trial design and management that sponsors must consider to maximize the likelihood of study success.
Introduction

By their very nature, clinical trials in rare and ultra-rare diseases are inherently challenging due to the very limited number of patients eligible to participate in the study. As a result, country and site selection are often constrained by where the patients are being treated, requiring sponsors to navigate a complex web of considerations and concerns related to regulatory requirements, study design, patient recruitment and retention, study staff, and data quality.

In many cases, in order to enroll a sufficient number of patients, sponsors must prepare to open sites in countries where clinical trials are uncommon and site or investigator experience is limited. Opening sites in these countries requires detailed knowledge of the host countries and the complex regulations they may impose, along with thorough training of sites and investigators on the study protocol and good clinical practices (GCP). In addition, study monitoring and trial oversight must focus on shepherding every patient through the study with minimal protocol deviations or other issues to ensure data integrity and statistical significance.

In this paper, we provide an overview of the issues sponsors must address at different stages of the study life cycle and offer strategies for ensuring that every patient – and every data point – counts in a rare disease clinical trial.
Selecting countries and sites

Identifying and setting up investigative sites are among the most difficult factors of conducting rare disease trials. While the U.S. and countries in Western Europe are still the most common centers for conducting clinical trials, the restricted availability of patients with rare and ultra-rare diseases, along with patient recruitment delays and poor investigator-driven enrollment, has prompted sponsors to open clinical trials in an increasing number of countries outside of these two regions. However, differences in patient populations, local regulatory and ethical guidelines, standards of care and the number and experience of available sites and investigators make global studies of any indication, much less a rare disease indication, a complex challenge.

Selecting the right countries and sites can have a widespread, positive impact on the efficiency of resource allocation and the likelihood of study completion. Important country and site considerations sponsors should take into account include:

+ **Regulatory framework.** Regulatory guidelines and ethical requirements may differ from country to country, or even among regions within a country.

+ **Import/export requirements.** Countries may have complicated import/export requirements, particularly with regard to the shipment of investigational products.

+ **Standard of care.** When planning a rare disease clinical trial, it is critical for sponsors and study planning teams to be aware of the current global-, region-, and country-specific standards of care with regard to the indication(s) under investigation. Existing treatment patterns and guidelines for the disease of interest may vary widely from country to country, and the specialist and site type may differ, as well. For example, in some areas, pediatric patients with rare diseases may be seen by adult specialists due to the low incidence of the disease. In other areas, patients with rare diseases may be referred to a central site to be evaluated by a key specialist. Thus, factors related to standard of care and associated patient pathways can have a significant impact on site selection, the clinical trial experience of site investigators, and the potential for patient recruitment.

+ **Travel restrictions.** Some countries, such as Iran, do not allow FDA inspectors to travel to investigative sites. Therefore, if using a site that imposes travel restrictions, sponsors must ensure that the quality of data and documentation is sufficiently rigorous to meet FDA requirements. In addition, face-to-face investigator meetings must be conducted in a country where the sponsor and all participating sites can travel freely.

+ **Site and patient reimbursement.** Countries may have widely different regulations and processes for site and patient reimbursement that need to comply with both GCP and local regulatory and ethical guidelines.

Sponsors should also factor in the availability of local staff to manage these considerations.
Recruiting and retaining patients

Before making the decision to open a country or a site, sponsors should make every effort to identify patients with the rare disease under investigation and ensure that those patients will qualify for the study before approving the site. This step can avoid unnecessary expenditures of time and expense in opening a site where no patient will be enrolled. Ultimately, the goal is to enroll all patients identified for the study, if possible, and to ensure that these patients complete the study with a minimum number of protocol deviations and extremely high data quality.

Patient identification

In the early stages of study planning, it is important to develop a detailed patient recruitment plan that takes into account the various patient pathways at each of the identified sites. A patient pathway is the route by which a patient is connected to an investigator at a specific site, whether it is by referral, the emergency room, or some other method.

If the patients are already known to the sites, site databases may be the primary source of patients. Existing patient registries can be extremely useful, as well. Sponsors may also identify and connect with patient advocacy groups, who are typically eager to offer assistance, such as posting the details of the study on their website, in exchange for a nominal administrative fee. Patient support groups are key in identifying and contacting patients, and often know of equivalent groups in other countries. They may also be useful for identifying clinical or research experts and current treatment centers that could assist with the trial.

In situations where patients are not known to the sites, different types of advertisement – digital ads, social media, dedicated trial websites, etc. – may need to be considered. This is especially true if the patient population is hidden, as can occur in rare diseases with late onset which may be misdiagnosed or in rare diseases which lead to symptoms, such as fecal incontinence, that patients may be reluctant to talk about. If utilizing a patient recruitment company to assist in these efforts, sponsors should vet the company’s experience in the specific indication under investigation and understand what type of approach will be most effective in promoting patient enrollment.

Another strategy that may be included in a patient recruitment plan is the creation of a strong study identity, whether it is a memorable name, brand, color scheme, tagline or marketing approach (e.g., masculine colors and language for a clinical trial on a disease that only affects men). This study identity should be meaningful to the patient and/or site staff, so they will be reminded instantly of the trial’s indication and objectives. This strategy is particularly important in studies that will enroll over a long period of time, with a limited number of patients expected per site.

Patient enrollment

Given the limited number of patients available, it is not uncommon to anticipate just one patient per site in an ultra-rare disease study. Therefore, there is no room for error when sites enroll their first patients. To minimize the risk for mistakes, sites should be trained thoroughly during both the investigator meeting (IM) and site initiation visit (SIV). If a long period of time has elapsed between the IM and SIV, it may be a good idea to perform refresher training. It is also recommended that the clinical research associate (CRA) is available at the site to support study staff either on the day of enrollment or as soon as possible thereafter.

The consent process for a rare disease study is a vital component of the enrollment process. Ensuring that the patient has a firm grasp of the study requirements can help to improve compliance and avoid early termination.
Since enrollment in a rare disease study is often difficult to predict, sponsors are advised to make contingency plans for patient recruitment, if possible. Examples of contingency plans include the identification of back-up countries or sites, or a marketing campaign to raise study awareness.

**Patient retention**
For rare disease studies, there is often an urgent or unmet medical need that gives patients an innate motivation to continue on the study. Nevertheless, it is still extremely important to pay close attention to providing appropriate patient and family support and eliminating as much of the study burden as possible. Sponsors may take exceptional measures to ensure that patients are able to participate – and stay – in the trial. These measures might include:

+ **Arranging for patient travel.** In addition to providing reimbursement for standard out-of-pocket expenses, such as meals and local travel, which may be required by some institutional review boards (IRBs)/ethics committees (ECs) for certain indications, it may be necessary to provide long distance travel and/or relocation costs for patients and their families to travel from their homes to a faraway center of excellence. For example, a patient and his/her family may need to be flown from the Middle East to a treatment center in the U.K., and then flown home again when the treatment is completed. The logistics are complicated, and regulations may require approvals from ethics committees in both countries, but study success may hinge on managing this process effectively. To that end, sponsors of rare disease studies should be sure to incorporate travel support into the study budget.

+ **Minimizing out-of-pocket expenses.** Supporting the patient and his/her family so they have little to no out-of-pocket expenses related to study participation can help to keep patients in the study. It may be wise to create a process for timely reimbursement of study-related expenses.

+ **Arranging home visits by a study nurse.** In addition to minimizing the burden of clinical trial participation on patients and their families, home care services may also be an effective measure for saving both time and expense for the sponsor. For example, in trials where injection of the investigational product (IP) is required, having a home care nurse train patients to self-administer the IP reduces the number of at-home visits required, as long as the patient is able to comply with the study guidelines. Experience has shown that patients and caregivers are better able to develop self-administration techniques and overcome any fear they may have of injections when their injection training is done in the comfort of their own home. In-home training can be supplemented with an instructional DVD on self-injections.

It is also important to find a good balance between protocol requirements and patient participation, e.g., weighing the number of clinic visits and time on site against the inconvenience and expense associated with travel. If travel is extremely difficult from a logistical or cost standpoint, sponsors may want to consider opening a site that is closer to where the patient lives.

**Selecting and training study staff**

**Site and investigator training**
While many rare disease trials are conducted at large academic institutions with extensive research experience, rare disease investigators often do not have hands-on experience with industry-sponsored research. The need for thorough and effective site training in rare disease studies cannot be overemphasized, as not only every patient, but also every data point is key. Thus, sites must have a comprehensive understanding of the study requirements prior to enrolling their first patient and need to maintain the same compliance and quality of data throughout the duration of the study.
In-depth study training is the cornerstone of a high-quality site and, for rare disease studies, it is highly recommended that sponsors employ face-to-face investigator meetings for training on the protocol, GCP, and specific study procedures, including blood collection and IP management. Sponsors should also consider recorded training sessions so that they can be used on-demand as refresher courses or to train new site staff. For longer studies, additional investigator meetings, webinars and other scheduled or ad hoc meetings may be useful for maintaining interest among the sites.

Building a strong relationship between the CRA and the site may help site staff to feel more confident in the study protocol. That said, it is important to establish appropriate levels of communication between the sponsor and the site at different time periods in the life cycle of the study. While communication is more frequent and intense during study start-up and patient enrollment, it may scale back during slower parts of the study, but should always be sufficient to keep the sites engaged.

**CRA selection**

Every rare disease study is going to have unique complexities and challenges, whether it is the patient population under investigation (e.g., pediatrics), the procedures involved (e.g., specialty laboratory tests or home care visits), or the breadth of geographies that need to be covered to locate patients. Each of these different study characteristics may have an impact on the requirements for a study’s CRA team. According to Anji Enmyeche, Director of Global Resourcing at Premier Research, the key skills to look for when assigning CRAs to rare disease studies include:

+ **Critical thinking skills.** CRAs do more than simply check data. They need to understand how to solve a problem, who to contact for guidance on complex issues, and when to involve the sponsor, all while protecting the regulatory stringency of the trial.

+ **Experience monitoring studies in complex indications.** Since rare diseases are rare, clinical experience in them is rare, as well. Sponsors should take care to select CRAs who can quickly learn the nuances of a rare disease patient population and their treatment. If possible, CRAs should receive specific training on working in rare disease studies. It may also be useful to train CRAs on dealing with sites that have never participated in industry-sponsored research.

+ **Confidence.** To be helpful to sites, CRAs need to be able to provide confident guidance to key opinion leaders (KOLs) and their staff and to navigate the complexities of academic centers without feeling intimidated.

It may also be important for sponsors to partner with a flexible organization that has the global reach to provide quality monitors in the countries of interest.

**Data monitoring**

In rare disease studies, closely managing data completeness, data quality and protocol violations is perhaps the most critical topic covered during monitor training. With very few eligible study patients, every patient counts and it is critical to take every possible measure to ensure that all patient data is usable for the analysis. Therefore, CRAs, clinical and data management staff must carefully monitor any trends or risk to the data (e.g., missing endpoint data) so that follow-up training and corrective and/or preventive actions can be implemented in response to any findings.

Many rare disease studies have frequent data and safety monitoring board (DSMB) meetings; therefore, timely data entry is increasingly important. Sites should be trained that data must be entered within 48 to 72 hours of the actual subject visit. In order to monitor site performance, sponsors may want to develop and track metrics for site responsiveness, such as timeliness in answering queries.
Sponsors should keep in mind that the data monitoring strategy implemented at the beginning of a trial is unlikely to remain static for the life of the study. Some sites will not perform as well as expected; others will surpass projections. Site staff turnover may change the performance of sites throughout the study. No single strategy will be able to predict and account for the dynamics of real-world clinical trials. Thus, the monitoring plan must have periodic re-evaluation built into it for the duration of the clinical trial program. When using a contract research organization (CRO), it is recommended to use a pool of monitoring visits rather than set times to ensure that monitoring visits can be scheduled when needed, rather than having a strict schedule, e.g., every six to eight weeks.

**Protocol considerations**

The protocol for a rare disease study needs to be well-reviewed to minimize the number of protocol amendments, especially with regard to changes in data collection for a limited number of patients. To develop a strong protocol for a rare disease, it is important to solicit input from KOLs, as well as patient organizations and/or advocacy groups. It is also important to keep in mind that the standard of care for rare diseases can vary significantly in different parts of the world and these differences should be accounted for in the protocol, if applicable.

**Third party considerations**

While the actual process of third party vendor management is no different for rare disease studies than it is for other types of studies, there are often more vendors to manage in a rare disease study. A number of niche vendors may need to be engaged to handle study logistics and procedures such as patient travel arrangements, home health care visits, specialty labs, physical therapists, imaging labs, central raters, and patient payment vendors. Examples of niche vendors include:

+ **Supplies**: The need for ancillary supplies in rare disease is dependent on the disease, study design, endpoints, and study drug. Specialized testing or investigational products in rare disease studies may require additional equipment be provided to the sites.

+ **Home care services**: Home care services are becoming more widely used in rare disease trials to minimize the burden of clinical trial participation on patients and their families, especially when patients may live quite far from the key hospitals/tertiary care centers where the study is being run. These services support at-home visits, sample and data collections and study drug administration. If including home health services in the study plan, sponsors should ensure that
the home care providers are trained on study requirements and GCP so that the protocol is followed and data is collected in a usable manner, all while adhering to clinical trial regulations.

+ **Patient payments:** It can also be useful to work with a patient payment vendor that provides a credit/debit card to pay subjects their study stipend so that the patient has no long-term out-of-pocket expenses for study participation.

**Conclusion**

While the nature of rare diseases creates specific challenges for clinical trial design and patient recruitment and retention, early planning that takes into account the many variables associated with having a very limited pool of eligible participants can help to mitigate risk and support study completion. Collaboration with a CRO that has regional experience and expertise in rare diseases may help sponsors identify and account for all contingencies in each stage of the study lifecycle, from protocol development and site selection, to first patient enrollment and study close-out. By taking into consideration the limitations and opportunities of rare disease trials, and addressing them appropriately, sponsors can help to ensure that every patient counts.

**References**

1. Premier Research. Rare disease and orphan drug survey. Data available upon request.
Alison Sampson, Ph.D. | Senior Project Director

Alison Sampson has over 20 years of clinical research experience including roles as CRA, project manager, senior project manager and project director covering Phase I – IV global studies. As an experienced project manager, she has led both clinical and cross-functional teams. She has worked in all phases of clinical research (I-IV) including global Phase III studies as the global project manager. She has experience in a wide variety of therapeutic areas with particular expertise in oncology, medical devices, and rare diseases in pediatrics and neonates. Her work experience includes roles in biotechs, blue chip pharma, and CROs.

Prior to entering clinical research, Dr. Sampson trained as a chemist and she is a Chartered Member of the Royal Society of Chemistry. She achieved Chartered Scientist Status in February 2009 through the Institute of Clinical Research.

Hanna Wide, M.Sc. | Project Manager

Hanna Wide has over eight years’ experience of project management of clinical research and a large portion of her professional career has been dedicated to rare indications. She has worked as program and project manager for clinical trials in rare indication, including both adult and paediatric populations. She has worked on global studies with significant experience of working in the MENA (Middle East North Africa) region.

Hanna has been involved in rare disease feasibility, protocol review, study and program management, CRF review, management of the clinical team, vendor management, and a range of other activities.

Hanna has a Master of Science in Medical Biology from Linkoping University, Sweden, and prior to joining Premier Research, Hanna has worked in Clinical Research Project Management at QED Clinical Services (a niche CRO specialised in rare indications) and Quintiles.

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