Creating Patient-Centric Clinical Trials in Rare Disease

A Guide for Sponsors, Contract Research Organizations, and Clinical Trial Sites.

This guide explores specific opportunities for sponsors, CROs, and trial sites to develop patient-centric clinical trials for rare diseases. For sponsors and CROs, patient engagement is critical. The patient perspective should inform every aspect of trial design and planning, including study design and clinical protocol writing, patient-facing documents, the potential use of digital solutions, home visits and telemedicine, and home delivery of medications. When it comes to trial sites, a patient-centric focus means considering key issues including transportation and lodging, home nursing, and budgeting.

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Introduction: Humanizing the Research Process

Clinical trials are an essential component of rare disease research, focused on patients who often struggle with genetic conditions and late diagnoses, a lack of specialists near where they live, and few, if any, options for treatments and cures. Rare disease patients, along with their families and caregivers, are desperately searching for help. According to the World Economic Forum, more than 95% of rare diseases lack an available treatment, and since 50-75% of rare diseases begin in childhood, the result is that one-third of children with a rare disease die before they turn five.

Sponsors researching new drugs to treat rare diseases can improve the quality of life and provide a positive clinical impact to patients. But rare disease clinical trials are challenging for many reasons. First and foremost, the number of patients who can participate in a rare disease clinical trial is, by nature, limited. In the United States, a rare disease is defined as affecting fewer than 200,000 people, and over 7,000 rare diseases affect more than 30 million people. In the European Union, a rare disease is one that affects no more than one person in 2,000; between 6,000 and 8,000 rare diseases affect an estimated 30 million people.

Not only is the number of rare disease patients limited, but also the number of medical experts with expertise in specific rare diseases is often very small and, in some cases, is limited to only a handful of medical experts globally. Some rare disease patients travel to other countries to participate in clinical trials, which carries great expense, potential loss of income, and significant logistical problems depending on the disease state. This is especially true of pediatric trials, where children and adolescents require the support of parents and caregivers who must also balance work, finances, and other family obligations. Patients and caregivers must also manage the requirements of the trial, including such potential issues as frequent blood draws, regular visits to the trial site, challenging technology, and more.

Anything that sponsors, Contract Research Organizations (CROs), trial sites, and other key stakeholders can do to minimize the barrier of entry for these patients and their families and caregivers, while also reducing the burden of trial participation for all parties and making it the best experience possible, is critical. Developing a patient-centric clinical trial is to make it truly possible for patients to participate; not just to enroll, but to remain throughout the course of the trial. A patient-centric trial is also feasible for caregivers, who are often intimately involved in most aspects of disease management.

It's easy to focus solely on recruitment, especially in rare diseases where the patient population is so small. But retention is also crucial and arguably more critical; a trial will fail if participants are unable to complete the process. A patient-centric trial enables patients to participate throughout the duration. For example, a sponsor might spend time and money to enroll ten subjects into a late-stage trial, knowing that the related regulatory agency will approve the drug if the outcome is favorable. But some patients drop out because they can't perform the required protocol-related procedures, such as entering self-reported data into an application and having blood drawn at regular intervals, or because they underestimate the time and travel commitment and cannot continue to afford lodging near the trial site. Therefore, the sponsor doesn't collect sufficient meaningful data, and can't move forward with approval. The chance of failure is significant in an industry where the risk of developing a new drug is already high.

A rare disease clinical trial which is not designed in collaboration with patients and caregivers nor well adapted to meet their needs is in danger of failure. The result is that a sponsor cannot move forward with a drug that could improve quality of life or even save lives. All the players involved in clinical trials, including patients, industry sponsors, CROs, trial sites, and Patient Advocacy Groups (PAGs), should commit to making trials patient-centric.

This guide explores specific opportunities for sponsors, CROs, and trial sites to develop patient-centric clinical trials for rare diseases. For sponsors and CROs, patient engagement is critical. The patient perspective should inform every aspect of trial design and planning, including study design and clinical protocol writing, patient-facing documents, the potential use of digital solutions, home visits and telemedicine, and home delivery of medications. When it comes to trial sites, a patient-centric focus means considering key issues including transportation and lodging, home nursing, and budgeting.

Sponsors and Contract Research Organizations

CROs help sponsors design and manage clinical trials, including data collection and reporting to regulatory authorities. Together, they have an opportunity to ensure that trials are more patient-centric. A CRO engaged in rare disease research should act as a partner to patients, caregivers, and the sponsor in promoting patient engagement to ensure that patient input is included throughout the design and execution of a clinical trial. Patient engagement which starts at the very outset of study design proves invaluable to the success of a clinical trial. Even if trial protocols are finalized, it's never too late to connect with patients, and in fact, it's vital to success, especially in rare disease. Understandably, the sponsor and CRO often focus on time to market and the trial enrollment rate, but taking an extra month or two to incorporate the patient perspective will pay off in the long run.

It is important for a sponsor to select a CRO that takes a 360-degree approach to client needs, with patients at the center. This CRO may work alongside the sponsor to engage with a network of PAGs focused on rare disease to support the design and execution of the study, build relationships with trial sites, and develop digital health solutions that meet the needs of patients, among other benefits. All of these factors should be carefully considered by a sponsor company during the CRO selection process and continuously evaluated as performance metrics during the study.

Patient Advisory Boards

Rare disease patients make it a priority to become educated about their disease because it's usually not well understood clinically. Therefore, they are a vital source of information, especially when it comes to designing an accessible clinical trial. To involve patients right from the start, a sponsor can form Patient Advisory Boards (PABs), a panel of patients (generally five to eight) living with the target disease who provide first-hand insight to inform and enrich product development and testing. Patients can provide input into the design of clinical trials, including the assessments and the endpoints of a trial, highlighting what is most meaningful to them. If patients are involved in evaluating the real-life feasibility of clinical protocols, the trial will better suit their needs. After the trial ends, the PAB can help assess the content and format of the lay summary. The PAB also enables sponsors to assess whether potential digital tools and wearable devices that may be used for the trial are suitable for trial participants.

For many rare disease indications, it is appropriate to include caregivers and family members in the PAB, as these individuals often provide critical information which may drive protocol changes and other important study design considerations. In pediatric clinical trials, parents and caregivers are the main PAB participants, but sponsors can include adolescents and older children in a PAB, as they are often an active part of the assent and consent process and therefore may provide valuable insights. In these cases, Good Clinical Practice (GCP), ethic principles and children's rights and all related regulations related to pediatric research should be carefully followed.

Patient Advocacy Groups

PAGs are organizations that promote the needs and priorities of patients. To develop patient-centric trials, sponsors and CROs should collaborate with PAGs whenever possible, particularly in rare diseases where these groups are such a powerful resource. Two of the most active umbrella PAGs focused on rare disease research are the National Organization for Rare Disorders (NORD) in the US and EURORDIS in Europe. Collaborating with PAGs helps sponsors and CROs create accessible clinical trials for rare disease in a number of ways, including dispelling any negativity towards the pharmaceutical industry and building trust with patients so that they are willing to help. PAGs are a potential source of patient experts for the PAB and of input on trial design. PAGs can share information about the trial with their members and help create patient registries. PAGs can also fill in some of the accessibility gaps that aren't covered by the trial protocol; for example, they may facilitate communication between patients and trial sites by providing information regarding available clinical trials on their websites. Additionally, PAGs may provide insights into potential partners that could provide patients with transportation to and from a trial site. Collaborating with a PAG can result in a more patient-centric and successful trial.

Caregivers

As noted above, caregivers often play a significant role in making a clinical trial more accessible for patients and helping patients maintain participation in a trial once enrolled. Their role is particularly key in the case of pediatric patients and other vulnerable groups of patients (e.g., people with mental health conditions, elderly patients) because the caregiver can provide first-hand information to clinicians. In a way, caregivers are co-participants in the trial because they are involved in the majority of the trial components along with the patient participant. Caregivers are often involved in study procedures such as investigational product administration or administration assistance in the home setting, assisting with telehealth visits, providing transportation to and from study visits, and, perhaps most importantly, providing the critical emotional, physical, and social support which helps a patient enroll into and remain in a clinical trial. Caregivers are often a point of contact for physicians and study team members at the hospital or clinic location, which is a critical factor when considering what methods may be used to promote communication between the trial site and patient. Also, caregivers frequently provide information for Patient Reported Experience Measures (PREMs) and Quality of Life (QoL) scales.

As described above, the PAB, managed by the CRO or sponsor, and the PAGs, most of which include a large number of caregiver participants, are critical connections between caregivers, sponsor, and CRO. Caregiver input should be part of the decision-making and study design process to achieve a patient-centric clinical trial.

Remote Data Collection and Clinical Trial Devices

Home use devices and digital solutions can seem like a silver bullet for trials. A sponsor may decide that a smartwatch is the perfect device to use in a hybrid clinical trial where patients will provide critical trial data remotely. But what if the patient population has limited mobility or difficulty with fine motor skills? They will likely have trouble using the smartwatch. If a sponsor relies on a CRO with experience in patient-centric rare disease research, this CRO should provide guidance and assistance related to the proper selection of feasible devices. Devices and applications designed in a simple and straightforward manner, avoiding complex screens and interfaces where possible and ensuring minimal connectivity issues, are best. A CRO can make recommendations based on knowledge of the medical technology landscape and on input from physician collaborators and hospitals. Additionally, a CRO should support patients and caregivers with an internal or contracted IT resource that can address technology issues directly.

Coordination of Home Visits

Sending someone from the trial's healthcare team to the home to conduct assessments, take vitals, or administer a drug can help to make a trial more patient-centric; it's easier for the patient because they don't have to visit the trial site (often an impossibility for rare disease patients). The success of home visits can depend on the disease state, the age of the patient, and other factors, including psychological components. Some patients may welcome a home visit, but others may not be comfortable with a stranger entering their home, especially if that person will be performing an invasive procedure. The caregiver may also play a role, especially in rare diseases; they may feel overly protective of the patient, or they may feel that they can perform the necessary tasks themselves. A one-size-fits-all approach to patients may not be appropriate; some may prefer a site visit to a home visit. A PAB can help the sponsor and the CRO navigate these delicate issues, considering the patient and caregiver perspectives as well as an understanding of the specific rare disease and its impacts on day-to-day life.

Telemedicine

Like a home visit, telemedicine can make trials more patient-centric, especially for rare disease patients. But CROs that support the sponsor must not assume that the patients will have sufficient connectivity where they live (the sponsor will need to provide connectivity if the patient lacks it), or that they will know how to use or be physically able to use the technology. It may seem simple to ask patients to use a tablet and answer a video call, but that ability may depend on the disease state and patient age. If telemedicine is a major aspect of a trial, the CRO must understand how it will impact the patients. When patients are confused by technology or lack the ability to access it, they won't participate, and the trial suffers from that loss of potentially meaningful data. Also, potential bias is introduced into a study if participation is limited to patients with internet access. Often, the CRO can provide hybrid or multi-option solutions; for example, a particular trial visit may be offered in telemedicine format, with the option for patients who are not comfortable with remote visits to visit the trial site. The sponsor and/or CRO must address any connectivity issues, as noted above; for example, patients with limited connectivity can be provided with a mobile hotspot or similar device which provides them with internet access. Providing patients and caregivers with technical assistance is essential.

Home Delivery and Administration of Medications

CROs can sometimes send investigational medications to a patient's home for administration by the patient or the caregiver, or a nurse may administer the drug in the home. Home delivery and administration of medications can make a trial more accessible, but to be effective, the selected CRO must understand how the chosen approach will work for the patient. The CRO should review these questions if the patient or caregiver will administer the drug:

- Will they feel comfortable doing that and are they able to do it correctly?
- How does the caregiver feel about this new process that will become part of their day-to-day care routine?
- How will drug accountability, appropriate storage (including issues such as temperature control), and potential return/destruction be monitored and managed?
- How will the CRO provide emotional support to the caregiver throughout the trial, especially in situations where trial site visits are not included or are spaced widely apart during the trial?
- What equipment will the CRO need to provide to the patient and caregiver and how will the CRO educate them on the equipment's use?

If a nurse will administer the drug in the home, the same issues discussed in the telemedicine section apply. Home delivery and administration may not be the best option if patients are more comfortable in a clinical setting. They may prefer to receive the first dose at the trial site in order to feel comfortable taking the drug at home. Or a home visit from a nurse might help alleviate any concerns. The nurse can also act as an additional resource for information, which can be valuable for patients, caregivers, the sponsor, and the CRO.

Home delivery and administration is further complicated by the issue of compliance; the site and the CRO must verify that the patient is taking the investigational medication as directed. A nurse conducting a home visit may count used vials or empty pill bottles and can speak with the patient and/or caregiver about their concerns and issues regarding the medication, as empty or used containers may not represent the patient's ability or willingness to take the medication as directed. The patient or caregiver could enter information into an app each time medication is administered, but again, that relies on the patient or caregiver's technical ability. Understanding the patient and caregiver perspectives and the state of the disease is crucial when it comes to interacting with the patient at home. To successfully answer the questions noted above, patients and caregivers must be involved in the study design process from the beginning.

As patient safety is the most critical consideration when designing a trial, the sponsor, CRO, and other stakeholders must ensure that any home visit, drug administration, or other trial component is safe and appropriate based on the nature of the patient population and the investigational product, including potential side effects (both short- and long-term).

Clinical Trial Sites

Clinical trial sites, including academic medical centers, hospitals, and clinics, provide further opportunities to develop patient-centric trials. Patients may visit a trial site to enroll in a trial, have medical tests, receive the medicine or medical device being tested, and have regularly scheduled exams. It's important to consider the patients' perspective and their ability to participate throughout the course of the trial. Trial sites are the main point of contact for patients; therefore, site personnel can provide a CRO and sponsor with useful insight into any challenging aspects of a trial for their specific pool of patients.

Home Nursing

Home nursing during a clinical trial can be beneficial, especially for trials that require frequent blood draws to vigilantly monitor patient safety. And rather than having the patient travel to the site just to draw two or three samples, home nursing can make a trial more accessible by bringing necessary testing to the patient. Of course, this raises the question of how individual patients respond to having a stranger in their home, as discussed above. Also, home nursing can be an expensive part of clinical trials and is sometimes one of the highest costs if frequent visits are required. Trial sites must leverage home nursing carefully, with the goal of making the trial more comfortable for patients, and must incorporate the patient voice in any home nursing aspect of the trial design.

When home nursing is included in the study design, the trial site must clearly define and establish the role of the home nurse at the outset of the trial. The qualifications (both education/training and previous trial experience) and the identity of the person performing the home visits may change depending on the nature of the trial. For example, in pediatric clinical trials, it is important for the home nurse to have previous experience in the care of the pediatric patient population. For all trials, it is essential that home nurses receive full training in GCP and are certified, not only as nurses, but in the conduct of clinical trials, including all related regulations and procedures.

Transportation and Lodging Costs and Logistics

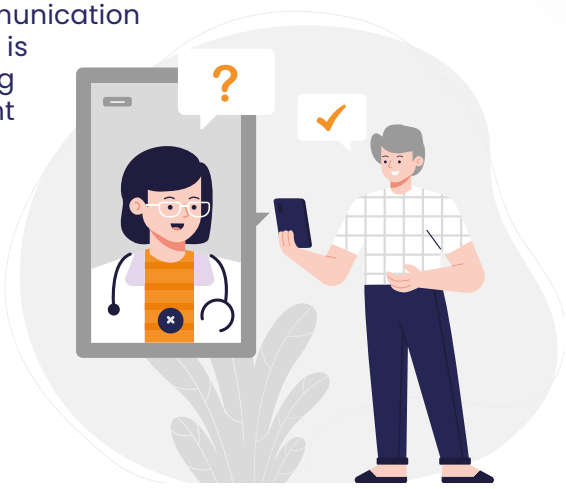
If patients must stay near the trial site for any length of time, the cost of transportation and lodging can create a barrier to accessibility. The patient's ability also comes into play; if the patient has mobility issues, for example, they may require accommodation on the first floor or in a building with an elevator. During the trial design phase, the trial site, in conjunction with patients and caregivers, must also factor in transportation between the site and the hotel. Some patients may require specialized transport, such as an ambulance or other larger vehicle to accommodate mobility issues.

Sites should consider developing relationships with local hotels for discounted lodging. PAGs can also help trial participants. For example, the American Cancer Society maintains Hope Lodge® communities across the country for patients and caregivers. For rare diseases with fewer resources, this may not be an option, but working with PAGs to uncover ways to support patients can help make a trial more accessible.

If a trial site has affiliated satellite centers or other referral centers within an appropriate radius, they can use these locations to make the trial more accessible. Though this may be an additional cost and logistical issue for sponsors and CROs, allowing a patient to receive care and study procedures at a satellite site can make a major difference to patient participation. This is should be considered early in the study design phase when identifying and selecting trial sites.

Resources for Patient Support

By providing support and resources for patients, trial sites can help make a trial patient-centric. Follow-up support like phone calls or other communications between site visits to discuss any patient concerns and check in on potential side effects are a great way to stay engaged with patients and retain them in the trial. Communication can make patients feel like their safety and well-being is a priority and that their concerns matter to those running the trial. But the best sites are the ones that take patient communication above and beyond, even when not technically required by the protocol, to provide much-needed emotional support to patients and caregivers. This attention can make the difference in a patient showing up for appointments or even staying in the trial. The CRO selected by the sponsor can also provide support to the site; for example, if the site team wants an external on-site coordinator or a calendar with automatic reminders about patient communication. The CRO should discuss ideas for support with the site team to agree on what would be helpful.



Budgeting

A trial budget is another opportunity to be patient-centric by including costs such as patients' travel, home visits, and medication delivery. Patient stipends should also be a consideration, especially in a placebo-controlled trial where a patient isn't guaranteed to receive an active study drug. Particularly in the rare disease community, patient participation is often difficult; ensuring that patients feel adequately compensated for the time and energy they're putting into the trial can make a difference.

Conclusion

Rare disease patients and their families and caregivers are under intense pressure as they seek solutions. To participate in clinical trials, they must take time off, sometimes travel great distances and cross borders, and spend extended periods of time devoted to this purpose. The hardships are extensive. And when the trial begins, the trial protocols may not work for patients.

When it comes to rare diseases, the patient perspective is invaluable. It is vital that all the players involved in clinical trials commit to making trials patient-centric. The selection of an experienced CRO and the right trial sites play an important part in this process.

Every clinical trial is different because every patient population is different, and a one-size-fits-all approach does not work. Depending on the type of trial, the phase, and the type of disease, sponsors, CROs, and trial sites can adapt trials to home visits, telemedicine, or both, using a hybrid format which combines remote and in-person hospital visits. A varied schedule that suits patient needs will best facilitate adherence to the trial, taking into account the unique needs of the patient, including disease, age, level of support, and other important factors. Trial sites should consider key issues including transportation and lodging, home nursing, and budgeting.

Sponsors and CROs must involve patients and their families/caregivers throughout the process of drug development. Ultimately, the goal is a patient-centric trial that enables the sponsor, CRO, and trial sites to recruit and retain enough patients to meet regulatory requirements and, ultimately, to bring valuable rare disease treatments rare disease treatments to the people who need them.