Advanced Clinical

WHITEPAPER

Making Rare Disease Clinical Trials More Patient- and Site-Centric: Learnings to reduce study burdens for key stakeholders

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Abstract

Rare disease patients and caregivers often face obstacles to participating in clinical trials; these obstacles include challenges in obtaining a diagnosis, lack of awareness of patients and healthcare professionals of rare disease studies, and specific resources to find them. Industry professionals are increasingly deploying innovative approaches to identify rare disease patients in order to enable them to actively engage and participate in clinical research. This paper discusses insights from a survey and webinar for incorporating the perspectives of rare disease patients, caregivers, and health care professionals (HCPs) into clinical trials.[1]

Introduction

Rare diseases affect 3.5-5.9% of the world's population or some 300 million people.[2] There are over 7,000 clinically defined rare diseases; of these, 72% are genetic and 70% start in childhood (see Sidebar 1).[3] There is a large unmet need within rare diseases – more than 90% are without an FDA approved treatment.[4] Clinical trials are of great importance as they are often the only route to find a suitable treatment and help meet the medical needs of rare disease patients.

The global rare diseases treatment market size was valued at $119.6 billion in 2021 and is expected to expand at a compound annual growth rate (CAGR) of 12.8% from 2022 to 2030.

To gain further insight into the perspective of rare disease patients – as well as enhance their experience participating in clinical research – Advanced Clinical partnered on an online global survey with Know Rare, a company dedicated to connecting patients with clinical research.[6] The survey was sent to people in Know Rare's database, capturing clinical research study insights from rare disease patients, caregivers, and health care professionals (HCPs). Sixty-seven respondents started the online global survey, which was launched on February 16, 2023, and 65 completed the survey. Of these, 88% (57) were rare disease patients, 8% (5) were caregivers and 5% (3) were HCPs. Key findings from the survey are shown in Sidebar 2, with more details provided in Sidebar 3.

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Sidebar 1: About Rare Diseases

- *300 million people worldwide or around 5% of the population are living with a rare disease Collectively, the number of people living with a rare disease is equivalent to the population of the world's third-largest country*
- *There are more than 7,000 rare diseases. More than 90% of rare diseases are still without an FDA approved treatment.,*
- *72% of rare diseases are genetic, while others are the result of infections (bacterial or viral), allergies and environmental causes, or are rare cancers; 70% of genetic rare diseases start in childhood*
- *There are an estimated 200 rare cancers. One in 5 cancers is rare and five-year survival rates are lower for rare cancers than for more common cancers*
- *In Europe, rare cancers are defined as those affecting less than 6 individuals per 100,000 per year; in the US, they are defined as affecting less than 15 per 100,000 per year [5]*
- *Equity for people living with a rare disease includes equitable access to diagnosis, treatment, healthcare, social care and opportunity*

There is a continued need to make rare disease studies less burdensome for both patients and sites, with potential areas of focus discussed below.

Improving Rare Disease Patient Centricity: Understanding Patient Perspectives

Rare disease patients often have a difficult diagnostic journey, resulting in these individuals and their caregivers typically being very well informed about their disease, and tending to direct their care much more actively than patients with more common diseases. They may also lack faith in the health care system due to this challenging journey.

The patient perspective is an essential element in designing a study with a minimal burden, helping the study to fit in with the patient's daily life as far as possible. Hybrid and decentralized clinical trials (DCTs) can help ease trial access for patients and may improve trial accessibility for those who live far from bricks-and-mortar sites; in the survey, 85% of respondents (53 out of 62) were interested in whether home visits were available as part of the study.

Patient support can be provided across the patient journey and treatment pathway using a combination of in-person and virtual touchpoints, such as telemedicine visits. As well as being potentially more convenient for patients and families, home visits may provide more insight into the daily lives of rare disease patients, including the challenges they face and any issues regarding treatment adherence. In one study, patients with amyotrophic lateral sclerosis (ALS) conducted remote self-assessments as part of a feasibility study. This offered information about how patients felt about participating in the trial overall, focusing beyond treatment logistics alone. The study found that despite worsening disease-related outcomes, the patients had a positive view of the processes being followed. This helped assess how people with ALS might want to participate in a planned ALS study.[7]

Sidebar 2: Summary of survey insights

- **Study participation: 31% of survey respondents (19 out of 65) had participated in a clinical research study, while 69% of (43 out of 65) had not, mainly due to lack of awareness (56% or 24 out of 65)**
- **Willingness to participate in future research: 86% of respondents (52 out of 61) would be interested or very interested in a clinical study of a treatment for their rare disease; of those who had participated in clinical research, 95% (18 out of 19) said they would consider taking part in research again in the future.**
- **Willingness to participate in a study throughout the disease journey: 79% of respondents (49 out of 62) wanted to know about the option of clinical trials at any point in their journey, with 34% (21 out of 62) wanting to know at diagnosis, 39% (24 out of 62) at the start of treatment, 32% (20 out of 62) when the disease progresses or worsens, and 29% (18 out of 62) when there were no other options (multiple answers were allowed).**
- **Option to have virtual study visits: 85% (53 out of 62) thought it was very important or important to have home/virtual visits as options in the study design.**
- **Doing independent research to find out about studies: 71% of respondents (44 out of 62) said they had searched for information about a clinical study for themselves or their family member.**

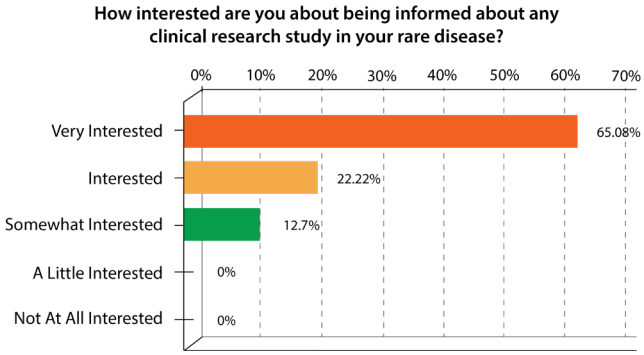
The patient perspective is an essential element in designing a study with a minimal burden.

‘Bringing The Heart’ to Rare Disease Trials

Building trusted relationships with patients and caregivers – or ‘bringing the heart’ to clinical trials – is key to patient-centricity in rare disease. Here, the burden of study participation to both patients and caregivers can be particularly great, depending on the symptoms and associated challenges of the particular disease. Rare disease trials often include procedures that may require long and/or frequent clinic visits. Minimizing this burden is essential, for example, by including only essential procedures and on-site visits in the protocol, and maximizing appropriate use of decentralized trial elements to enable remote participation.

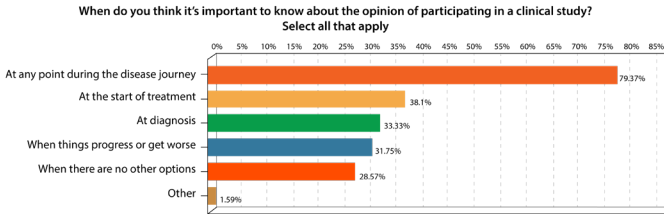
High Levels of Interest in Rare Disease Clinical Trials

A particularly encouraging finding from the survey was that **95% of respondents who had participated in a clinical research study (18 out of 19) said they would consider taking part in research again**, indicating that this was a positive experience. For the 69% of respondents (43 out of 62 who had not participated in a study, **lack of awareness of the existence of relevant clinical trials was given as a reason by more than half** (56% or 24 out of 43), with 28% (12 out of 43) saying that they did not know how to participate or what was involved, and 26% (11 out of 43) saying that their physician did not mention the option of a trial.



The survey indicated high levels of interest in rare disease clinical trials, with 86% of respondents (52 out of 61) saying they were interested or very interested in a clinical study for a potential new treatment. **Trials were of interest at any point in the rare disease journey, according to 76% of respondents** (37 out of 49). Sometimes, trial participation is viewed as a last resort, rather than being offered at the earliest possible stage of the disease, including at diagnosis. In the survey, 79% of patients (49 out of 62) said they were open to clinical trials at any point in their disease journey, with 34% (21 out of 62) wanting to know at diagnosis, 39% (24 out of 62) at the start of treatment, 32% (20 out of 62) when the disease progresses or worsens, and 29% (18 out of 62) when there were no other options. Multiple answers were allowed. **Clarity is needed to ensure that trials are not treated as a last resort by HCPs.**

When asked about important reasons to consider



participating in a clinical study, 71% (44 out of 62) wanted to help others and advance research of the disease and its treatment; and 52% (32 out of 62) and wanted to gain access to the latest treatment in development. Having access to study investigators – who are among the relatively few specialists in the rare disease area being studied – can be a major benefit to study participation, as identified by 63% of survey participants (39 out of 62). Having personalized care was mentioned by 48% (30 out of 62). Again, multiple answers were allowed.

Patient support groups, government websites and physicians are the most popular places for patients to seek out information about clinical research, followed by Google and other search engines, including social media. In the survey, **71% of participants (44 out of 62) agreed or strongly agreed that they would use a patient advocacy group or patient support group**; 69% (43 out of 62) would use government clinical research study websites (such as clinicaltrials.gov, Orpha.Net, and EudraCT); 60% (37 out of 62) would use Google or other search engines; **55% (34 out of 62) would ask a doctor**; and **47% (29 out of 62) would use social media channels such as Facebook and Instagram**. These preferences can be taken into account in efforts to improve awareness of ongoing studies.

Communicating the Care Taken to Protect Patient Safety

Safety is an ongoing concern among some potential study participants, accounting for some individuals deciding not to pursue clinical trial opportunities. Information about all aspects of participant safety should be included in materials supporting the trial, and should not be left until the patient arrives at the clinical site. By that point, many potential participants may have already been deterred from seeking more information.

Explaining the Role of Placebo and the Fact That Standard of Care is Normally Available

Potential participants are often worried about the possibility of receiving placebo. In the survey, 82% of respondents (51 out of 62) mentioned this as a concern. In reality, most rare disease trials look at the investigational therapy in addition to the current standard of care for the disease. This should be more clearly explained. Potential study participants also frequently ask whether they will be allowed to continue on the investigational therapy once the trial has been completed, via an open-label study. Making this option available is another way to be more patient centric, especially for larger sponsors whose budgets can accommodate this approach.

Another question often asked is whether the patient will be able to keep their own physician when they join the trial, due to a misunderstanding about the way trials work. **Questions also arise about whether study participants can continue taking current medications during a study (mentioned by 94% of survey respondents** (58 out of 62)); and what happens if they wish to leave the trial (mentioned by 73% (45 out of 62)). **Although these questions are addressed in the informed consent form, they should be addressed at the outset when patients are first considering participation, to help them better understand the process and support better-informed decisions.**

Including Patient-Centric Study Endpoints

Patients are also interested in what the study will measure. Laboratory findings are recognized as being informative, but patients are primarily interested in meaningful metrics that will reflect a positive impact on their symptoms and daily lives. Having a protocol that includes these types of outcomes helps improve the patient-centricity of the study and helps the patient better understand the impact new treatments might have upon their condition/symptoms. The U.S. U.S. Food and Drug Administration (FDA) requires a patient reported outcome as a primary outcome for therapeutic trials.

Considering Less Restrictive Inclusion/Exclusion Criteria

Study inclusion/exclusion criteria are often very stringent, targeting the healthiest possible people with a particular disease – the "healthy disease population" – who ideally do not have other conditions or need to take other medications. This is typical for RCTs (Randomized Clinical Trials), with the goal of minimizing confounding factors and yielding the highest quality data. However, this approach inevitably narrows the search within a rare disease population that is already, by its nature, very small. This is an important epidemiological feature to make sure that the results obtained can be explained by the treatment alone and not by any other confounding factor. RCTs are therefore the highest level of data. However, further studies using observational designs, registries etc. help to understand the effectiveness of the therapy in clinical practice. To improve patient-centricity, alternative study designs should be considered, taking account of the realities of the patient population, who may have other conditions and be taking other medications, in order to enable more individuals to take part in the study.

Using Technology to Improve the Patient Experience

Technology can help improve the patient experience by making it easier for them to participate – for example, by enabling virtual visits via telehealth and remote informed consent. Technology can also help gain timely access to records, a step that can cause delays and extra work for investigators and site staff. Endpoints and metrics gathered using wearables still need further investigation, validation and standardization. Challenges relating to interoperability also remain, including major differences between EMRs at various health systems. One option might be to create a portal where patients can upload health data, such as their latest lab results. These should be user friendly, with training and support freely available. Various methods of capturing accurate patient data and feedback that are appropriate for the patient profile should be considered and tested - for examples, pediatric trials might use simple emojis to capture patient outcomes – and they should, follow the same vigorous evaluation as any other approaches used for clinical trials.

Improving Site Centricity: The Challenges of Decentralized Trial Elements

A site-centric study protocol minimizes the burden to clinical research sites. As sites learned during the COVID-19 pandemic, the increasingly popular hybrid studies and DCTs pose multiple challenges that may differ from those faced with onsite trials.

Challenges may include restrictions in receiving information from home nursing visits, and scheduling patient visits by a third party. Data privacy regulations in both the European Union and United States can hinder access to medical records and data. In many cases, patients are required to submit a request for their data to be shared as part of a study. There is also a lack of standardization of electronic medical record (EMR) use in prescreening; virtual prescreening can be more appropriate for both sites and patients.

Due diligence is required to ensure that there are sufficient financial and other resources essential for the trial, for example, if there is a need to hire, train and retain staff to help execute clinical and administrative aspects of the trial (including contracts, budgets, recruitment calls, visit scheduling, patient reimbursement, and insurance review). Minimizing site burden is especially important in recruiting new sites in geographies with access to rare disease patients. Site management organizations (SMOs) can be helpful in providing support from a central business location; SMOs can do the groundwork in new regions, enabling sites to focus on seeing patients.

A major factor to keep in mind from both patient and site perspectives is the need to respect people's time. While virtual elements have the benefit of allowing remote participation, best practices are still being developed.

Considering DE&I in Rare Disease Clinical Trials

Rare disease patient populations are sparse by their very nature, making demographic diversity potentially less important than in trials involving more common diseases. However, some genetic conditions may be more prevalent in some ethnic groups, making inclusion of these groups essential.

Improving diversity in trials is the subject of April 2022 draft guidance document from the FDA. The draft guidance is titled, "Diversity Plans to Improve Enrollment of Participants From Underrepresented Racial and Ethnic Populations in Clinical Trials; Draft Guidance for Industry." [8,9,10] While encouraging enrollment of diverse clinical trial populations, this states that in certain situations, it may be challenging to set an enrollment goal based on the epidemiology of the disease due to limited data. In such cases, FDA encourages sponsors to set enrollment goals based on available data, such as published literature and real-world data. If not feasible, "it may be appropriate to set the enrollment goal based on demographics in the overall population with the disease or condition."[11]

Rare disease patient populations are sparse by their very nature, making demographic diversity potentially less important than in trials involving more common diseases. However, some genetic conditions may be more prevalent in some ethnic groups, making inclusion of these groups essential.

Conclusion

Most rare diseases do not have an approved treatment, so clinical trials are the major viable treatment option for many patients. This makes it important for patients to become aware of trials as early as possible following a diagnosis. Multiple new approaches are available to support effective rare disease patient engagement strategies and add value for sponsors, site staff, regulators and the patients themselves, who are in need of new treatments and care regimes. Based on the survey results, rare disease patients are interested in learning about and participating in clinical trials, yet often lack information on ongoing studies that are relevant to their condition. Many patients would be interested in participating in trials early on in their disease progression, rather than waiting until all other treatment options have been exhausted.

There is a clear need for study sponsors and CROs to improve engagement with patients, advocacy groups and HCPs to improve awareness of ongoing rare disease studies and what might be involved when participating in a study. Improved communications will also be key to answering questions and addressing misconceptions around patient safety, the role of placebo, and potential availability of open-label studies.

Other helpful approaches include making sure that study endpoints reflect patient priorities, broadening inclusion/exclusion criteria to enable more patients to participate, and applying technology in areas such as informed consent to minimize patient burden. From the site perspective, many of the challenges of implementing DCTs still need to be addressed, including solutions for data privacy and access to medical records for prescreening, plus the provision of appropriate financial and other resources for implementation. DCT elements have particular potential in improving clinical trial access for patients who may live long distances from bricks-and-mortar sites. Keeping in mind the need to be respectful of time requirements involved in trials from both patient and site perspectives – helping to minimize the burden and maximize the benefits for all stakeholders.

Sidebar 3: Survey findings: 95% of trial participants would consider taking part again

- Thirty-one percent of the survey respondents (19 out of 65) had participated in a clinical research study. Of these, **95% (18 out of 19) said they would consider taking part in research again.**
- Several questions were asked about information received by those who had participated in a study; **95% (18 out of 19) agreed or strongly agreed that the information they received before taking part prepared them for their study experience**; and 79% (15 out of 19) felt that they were kept updated at all times or moderately updated about the trial they were involved with. This suggests that once engaged with the trial, participants were largely satisfied that their information needs were met, although there is room for improvement in ongoing study-related information.
- When asked how supporting information was received in the study (multiple answers were allowed), **68% (13 out of 19) said information was provided in conversations with the study team**; and 32% (6 out of 19) received printed study materials. Again, this indicates a positive experience once engaged with the trial.
- When asked what could have made the research experience better (multiple answers were allowed), **47% (9 out of 19) respondents said that an app with all study information would have been helpful; 47% (9 out of 19) would have liked a study-related website**; 32% (6 out of 19) would have liked printed study-related materials; and 37% (7 out of 19) would have favored compensation for time off work, parking fees or food needed during study-related site visits. These elements could be incorporated in trials as a potential way to improve the study participant experience.
- **Lack of awareness of relevant clinical trials was a major factor identified by the 69% of respondents (43 out of 62) who had not participated in a study**; more than half (56% or 24 out of 43) gave this as a reason for not participating, followed by 26% (11 out of 43) who said their physician did not mention the option of a trial, and 28% (12 out of 43) who did not know how to participate or what was involved.
- **Potential study participants are interested in a wide range of topics relating to the trial**, including the phase of the trial, disease pathology and potential mechanism of action of the study drug, length of study, numbers of visits, and whether there is a placebo arm. Respondents gave “important” or “very important” ratings to: the study phase, chosen by 81% (50 out of 62); how the disease works, and how the different treatments may affect it, by 92% (57 out of 62); how long the study will last, how many visits are required, logistics of travel to the study site, by 97% (60 out of 62); whether all visits are at the site or can be virtual/at home, by 85% (53 out of 62); whether a placebo is given, and the chance of getting it, by 82% (51 out of 62); whether they can continue taking current medications during the study, by 94% (58 out of 62); and what happens if they change their minds and no longer want to participate, by 73% (45 out of 62).

Rebecca Starkie

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Much of Rebecca's 24-year career in clinical research has focused on strategy and running clinical studies, with experience in managing studies across a variety of rare disease studies and all phases. Her most recent experience has been specifically around Patient Engagement, supporting both clients and teams alike with strategies for recruiting and engaging patients. Passionate about bringing patient engagement to the forefront with an entrepreneurial mindset and liking to think outside of the box, Rebecca holds both a BSc (Hons) Biochemistry and a Certificate in Clinical Research from The University of Leeds, England, U.K.

Nina Wachsman

Founder & President, Know Rare

Nina has experience across many rare therapeutic categories from autoimmune diseases to rare cancers. Her expertise ranges from market research, strategy, to patient and digital marketing. She has experience in developing and leading programs from early-stage clinical trial recruitment and disease positioning through pre-launch and post-launch HCP engagement. Previously Nina founded and led a dedicated patient marketing division for the Interpublic Group.

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Upon graduating from Bangalore Medical College, India in 1984, she completed a neurology residency at the National Institute of Mental Health and Neuro Sciences, Bangalore, India in 1991. After moving to the US in 1995, she completed another neurology residency, and a fellowship in Neuromuscular Diseases at the University of Tennessee, Memphis, TN. A fellow of the American Academy of Neurology (AAN), she served as a member of the Guideline Development sub-committee of the AAN for 13 years.

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A clinical operations professional who has worked in the biopharmaceutical industry for more than 14 years. After 10 years of working in Manufacturing and R&D as a chemist, she decided to start a new career in Clinical Operations. Starting as a Clinical Trial Administrator (CTA), Clinical Research Associate (CRA), Trial Manager all the way to a Program Director managing various studies under multiple indications. She has worked both in CRO and biotech companies gaining experience in therapeutic areas such as cancer, hepatic rare diseases, and cardiovascular indications to name a few. She has helped build infrastructure and processes related to SOPs, TMF, vendor oversight and site management.

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