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WHITE PAPER

Listening to Rare Disease Patients and Caregivers:

A Wish List for Effective, Expedient Clinical Trials

Introduction

Because rare diseases are often severely debilitating, degenerative, and/or life-threatening, those conducting clinical research in rare disease therapy areas have an extraordinary mandate to integrate patient centricity into their clinical trials. Sponsors and their research partners must appreciate the differing challenges patients and caregivers in rare diseases face and find ways to accommodate their unique needs.

Efforts to find, enroll, and retain the participants needed to develop treatments for rare diseases must be accelerated and are acutely sensitive. This is especially true when addressing rare diseases in children, with half of all rare disease patients receiving their diagnosis before turning age 18. Thus, it behooves sponsors to gain deep insight into the patient perspective and to incorporate the findings into their trial designs and recruitment and retention strategies.

To understand the experiences of rare disease patients and their caregivers first-hand, Medidata convened a Patient Design Studio workshop of patients, caregivers, and patient advocates, focusing on clinical research in rare diseases. The workshop in June of 2022 included rare disease patients and representatives of patient advocacy groups. Participants used the discussion as an opportunity to voice issues that are often overlooked or unrecognized by the life-science industry. They presented their concerns as an appeal to researchers, clinicians, technologists, and data scientists to develop better solutions to meet numerous unmet or under-met needs of these oft-overlooked smaller communities.

Heeding the comments of rare disease patients, caregivers, and advocates can serve as a springboard to innovation and, ideally, could lead to a paradigm shift in how entire populations of patients are engaged in clinical research.

Disease Complexity Compounds Mental Health Conditions

Patients diagnosed with rare diseases may contend with limitations in their physical and cognitive functioning which in turn impacts their social interactions, communications abilities, and emotional well-being. It is not uncommon for rare disease patients to feel isolated, depressed, or emotionally drained. Research conducted by Rare Disease UK revealed that 95% of respondents have felt worried or anxious, 93% have felt stressed, 90% have felt low, 88% have felt emotionally exhausted, and 70% have felt at the breaking point. In the same study, 36% of patients and 19% of caregivers admitted to having suicidal thoughts.[1]

Against this backdrop, consider the burdensome factors for patients participating in a rare disease clinical trial:

- **Location of treatment centers.** Because fewer sites can conduct trials in rare diseases, patients often must travel great distances to treatment centers. This can mean uprooting the entire family to be close to a trial site, which can create high out-of-pocket expenses and cause housing and employment challenges. When the center is in another country, these families must acclimate to additional life challenges including an unfamiliar healthcare system, a new culture, and altered daily living.

- **Mobility challenges.** Many rare disease patients have mobility issues, and traveling can prove as burdensome as the treatment itself. The traveling time commitment of a trial taxes the entire patient/caregiver ecosystem, removing both parties from routines and placing an additional layer of stress on top of already-difficult medical care.

- **Medical criteria and healthcare activities.** Some eligibility criteria require medical steps that are particularly burdensome for pediatric populations. Simply requiring patients to visit sites can be stressful, affecting their physical abilities and their mental and emotional responses to clinical stimuli. This may directly affect the results of performance tests like the 6-minute walk test which can be more difficult and taxing in a clinical situation, affecting a patient's potential participation in a clinical study.

Not to be minimized is the extra work that trial participation means to caregivers. It frequently falls to them to coordinate trial obligations alongside other treatments, navigate insurance benefits and government assistance programs, explain the treatment, and stay abreast of developments.

> **"Rare disease forces you into poverty most of the time."**
>
> **"I'm lucky - most moms caring for a child with a rare disease can't work, or a marriage splits up."**

Ease Eligibility Criteria to Accelerate Approvals

Participants in the Patient Design Studio were keenly aware that clinical trials in rare disease areas are protracted, and they eagerly discussed the potential for improvement. Rare diseases can progress rapidly and many are so severe that they require urgent treatment.

Our Patient Design Studio participants repeatedly pointed out how sample size requirements can make enrollment a slow and difficult process, given the small numbers of patient populations and subpopulations. They emphasized that drawn-out enrollment ultimately delays the availability of treatment. Their plea was for sample size requirements to be relaxed and for sponsors and contract research organizations (CROs) to find ways to make small sample sizes sufficiently powerful. Bayesian statistical methods and in-silico trial concepts are evaluating whether they could be a solution to generate and enrich clinical trial data by simulating outcomes.

Participants also expressed frustration over the stringent inclusion/exclusion criteria that sponsors establish by targeting particular populations. Such criteria contribute to slow enrollment and, even more devastating for patients, can preclude patients from participating in a trial that could make the difference between life and death when there are no other treatment options.

The group discussed the value of collecting more biomarker data in natural history studies to understand the comprehensive disease in question better. Improving the efficiency of collecting this data could then inform more effective trial inclusion/exclusion criteria – ideally broadening the spectrum of who could be enrolled. It would also add to our understanding of treatment effects achieved in the trial itself.

> **"Does it really matter that my daughter is two months away from meeting the age requirement for a clinical trial that could save her life?"**

Use External Control Data to Eliminate Placebo Arms

As there could be ethical issues with placing rare disease patients into a control arm within a clinical trial, the use of external control arms was seen as a solution that could reduce, or even eliminate, the need to place trial participants on a placebo treatment. Relying on historical data as an external control also decreases the number of patients needed to conduct a trial and increases the number of patients to receive the potentially more promising intervention.

The problem, though, is that while rare diseases are ideal areas for using external control arms in clinical trials, the rarity of the conditions means that there may be little or no past trial information that can be used to populate the external control arm. In such situations, the hope is that regulators and data scientists would be able to use data from studies in other similar diseases/trials to develop the external control arm.

Cater to Patient Limitations with Decentralized Clinical Trials

The representatives in our Patient Design Studio strongly favored decentralized trial designs, as bringing the trial to the patient reduced many of the significant hurdles for trial participation for rare disease patients and their families. They identified the benefits of the flexibility and personalization of decentralized clinical trials (DCTs) as:

- Addressing the logistical and financial complications of traveling to treatment centers, increasing trial participation
- Lowering patient and caregiver stress by reducing the number of site visits through remote electronic data capture, sensor usage, or video visits
- Improving the validity of data. Many participants commented on the value of patient assessments at home vs. in a clinic – especially with pediatric populations. It was widely agreed that assessments performed in the real-world setting produced more authentic results than those performed at sites. Using videos taken at home and uploaded to the healthcare professional could be quite valuable in supporting such real-world assessment.

Using as many remote trial components as possible was seen as a win-win for patients and sponsors.

> **"I can't think of an area where decentralized clinical trials are more important."**

Improve Data Centralization and Portability

Data issues abound in rare disease therapy areas. A lack of quality data or an inability to access integrated data inhibits the quality of care and the advancement of research. While these challenges are present in other patient communities, they are exponentially more prominent for those battling rare diseases. The lack of data centralization limits our ability to glean insights into the bigger health picture at both the individual and population levels. Although some rare disease advocacy groups (particularly in ultra-rare diseases) already integrate multiple data sources (e.g., clinical trials, electronic health records, patients' self-monitoring, etc.) and open their data repositories for research purposes, not all do.

The Patient Design Studio group was impatient for the data that exists to be brought together in a way that would help those with rapidly progressing degenerative diseases. They recognized the need for infrastructure investments to centralize data and for competing data aggregators and patient advocacy groups to collaborate to achieve a common goal, overcoming an inclination to hoard data. Such collaborative steps would enable:

- **Researchers to share data.** The possibilities for expanding data collaboration would prompt more rapid, precise trials and support research into connections between mutations, genetics, and other diseases. It is currently challenging to crossmatch biomarkers with genetic information and the actual physical characteristics and symptoms that patients experience.

  One group member relayed an experience in which different researchers shared their data to examine the interplay between two different gene mutations that previously had not been associated with one another. This work led to them exploring an entirely new avenue of research. Data shared in this way could, conceivably, support the development of more broadly applicable therapies.

- **For Patients to understand their condition better and navigate the healthcare system more easily.** Currently, the burden is on patients/caregivers to ensure that all parties involved in the patient's care have received the proper information. They must self-monitor and manage their own data, including communications between separate healthcare providers and sites. At the same time, the patients we spoke with felt restricted in their access to providers' data on them and were hindered in transferring it to different providers during their treatment journey. Participants also yearned for the ability to benchmark their data against the broader trial data.

- **Healthcare professionals to gain a more comprehensive view of a patient's condition and care.** At the moment, patients often have to self-monitor and manage their data, including communications between separate providers and sites. The burden is now on the patient/caregiver to ensure each party has received the proper information. Data sharing across providers will allow each physician to gain a holistic view while avoiding possible duplication of tests.

The group acknowledged that the patient consent process needs to be rethought to pave the way for more data aggregation in a compliant, transparent, and beneficial manner. They advocated for building patient consent for de-identified data-sharing initiatives into the trial informed consent process.

They also saw giving patients and caregivers access to a single source of all trial-related information via one interface as a significant step forward. It is frustrating for patients and caregivers to switch between apps and interfaces; many just give up. Thus, there is a significant opportunity to increase data validity, improve the patient experience, and reduce the burden on the caregiver by streamlining the digital experience for patients/caregivers.

> **"The primary care physician who took care of me when I was first diagnosed died, and her husband most likely destroyed all her patient records. After finding out that I was misdiagnosed for eight years, I spent months searching for my data to no avail."**

Provide Additional Patient Education and Support

The members of the group stressed the challenges they face in understanding the science behind a rare disease and the implications for individual patients and their families. While it is often said that patients and caregivers become experts in their rare disease area – often to a greater degree than many clinicians – that knowledge is hard won. Clear, consistent communication and support are simple necessities for families participating in rare disease clinical research. More specifically, they need:

- Help in understanding the mechanics and benefits of clinical trial participation. Rare disease patients and their families need education on how clinical research works and on its benefits. Properly informed, they could decide to participate in research on more than an assessment of the burden involved. They also can use guidance on how to compare the investigative therapy to existing treatments and how to evaluate one trial vs. another so that they can make the most informed decision possible.

- Help in interpreting very complex and ever-evolving clinical information. Patients and caregivers can become confused by updated genetic information or when data from multiple sources finally coalesce. Geneticists, genetic counselors, and trusted advocacy groups can help patients navigate through their diagnostic odysseys with appropriate testing strategies and interpret their clinical findings, providing the depth of knowledge that can make a difference in treatment options and their efficacy.

> **"Doctors diagnose, nurses heal, and caregivers make sense of it all."**
> **– Brett H. Lewis**

Conclusion

Above all, rare disease patients and their caregivers seek empathy from biopharmaceutical researchers and the clinical trial industry – empathy that translates into consideration for their trial participation challenges and their urgent desire for effective treatment. As one of our group participants said in referring to a clinical trial, "This isn't a data farm for you; this is a patient experience."

Consideration should be given to the capabilities and limitations of the patient population when designing rare disease trials, as activities that would be considered standard or easily tolerable for patients in other therapy areas may be painful, taxing, or even impossible for those with a rare condition. This is especially true for pediatric populations. Thus, creating more patient-centric clinical trials can have a greater impact on patients with rare diseases than on other patient populations. There are so many areas in which patients with rare diseases have unique or specific needs that their input in trial design can be the difference between successful accrual and execution and trials that fail because of poor enrollment or poorly-designed data measures or endpoints.

The patients, caregivers, and advocates that we spoke with were appealing to the brilliant minds and problem solvers in the industry to "get it right." For them, that means not only easing the burdens of participation but also making it easier to qualify for studies and to gather and share information at the individual and population levels.

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