Registries in Rare Disease Research
Approaches to Optimize Success

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Advancements in gene therapy and transformative medicine have had a major impact on the development of treatments for rare diseases, resulting in a growing need for evidence of the safety, effectiveness, and value of these treatments in the real world. Opportunities to improve healthcare, clinical outcomes, and patient and caregiver quality of life are abundant, but for successful market access of novel treatments, robust – and frequently longitudinal – clinical and outcomes data from the usual care setting are necessary. A significant obstacle to collecting this data, however, is the low number of patients with the disease being studied. The US Food and Drug Administration (FDA) classifies a rare disease as any disease or condition affecting less than 200,000 patients in the US.[1] Hence, the identification and long-term engagement and retention of these patients is a primary challenge.

Registries can be an incredibly useful tool in gathering data on patient usual care, current treatment landscape(s), and long-term clinical outcomes, as well as other uses noted by recent FDA guidance,[2] to better understand the impact to the disease population and strategically plan for additional real-world patient research and treatment development. In observational, non-interventional registries, or disease-specific registries, used to gather real-world evidence, identifying, engaging, and enrolling as many of these rare disease patients as possible is vital to the success of the registry. One common challenge is convincing usual care physicians of the benefit of participation in these observational registries since no experimental drug is provided. In these cases, it is imperative to convey the importance of every real-world patient experience, particularly in rare diseases where there are so few patients available, and that every effort must be made to connect, involve, and embrace the opportunity to better understand the impact of treatments on patient outcomes outside of the clinical trial setting.

Success of a registry hinges largely on the study design, which can influence the operational aspects of the registry as well as patient engagement. The ability to operationalize the registry protocol is paramount – the best written


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protocol cannot be successful if it is not feasible within sites and with site staff. The protocol must be flexible to adhere to standard of care procedures; it must allow for variability in data collection as each treating clinician may conduct standard of care visits and document clinical information differently; and, lastly, it must not influence standard of care treatment for the patient – it must adhere to "the real-world" treatment paradigm. Although these key principles for real-world data collection must apply, there still exist inherent challenges to enrolling patients into registries, and even further challenges to enrolling patients into rare disease registries. How to best capture the patient data may depend on the protocol – disease-specific registries versus treatment-specific registries.

Treatment-Specific Registries

Treatment-specific registries are designed to enroll patients already receiving treatment, per physician intent. Therefore, all clinical data is associated to a specific product and focuses on treatment-specific clinical outcomes. The benefits of this study design are that it allows the audience to understand:

1. Focused demographics of patients diagnosed with the rare disease and prescribed the specific treatment
   - Is there a difference in the demographics of the patients receiving treatment and enrolled in the registry compared to the overall rare disease population as understood in published literature?
2. Clinical outcomes specific to the treatment
   - Are there clinical outcomes newly identified in the real world that were not identified during earlier clinical trials for the product?

Although registries would include all patients receiving treatment, there is a consideration that not all patients would consent to participate in the registry after receiving treatment as per usual care. Therefore, the population reflected in the treatment-specific registry would be a subset of the specific treatment population, which, of course, is associated with potential selection bias.

Key factors for increased treatment-specific registry engagement

Key patient recruitment and engagement initiatives that have proven to be successful in rare disease treatment-specific registries include:

1. Dual outreach and partnered communication by the sponsor and clinician to encourage patient participation
   - Developing direct-to-patient communications to highlight the value of participating in the registry
   - Coordinating sponsor partnership with advocacy group(s) and disseminating treatment-specific registry information via the advocacy group communication(s)
2. Sharing data results of the registry with the enrolled patient population
   - Sharing data results and helping the patient to better understand how his/her peers are responding to similar treatment helps patients feel engaged and empowered in managing their own care

Disease-Specific Registries

Disease-specific registries are designed to enroll "all-comers" of a rare disease into a registry. A patient with a diagnosis can be eligible for enrollment and ongoing observation within the registry without impacting standard of care treatment or schedules. The benefits of this study design are that it allows the audience to understand:

1. Demographics of patients impacted by the rare disease, regardless of treatment
   - Are there trends in race/ethnicity?
   - Is there a specific age range for diagnosis?
   - Are there socio-economic influences in rare disease diagnosis and treatment?
2. Current treatment landscape – insight into all of the treatment options patients with a specific rare disease have available to them
   - Are there specific treatment protocols/guidelines already established? Will new treatment approvals impact treatment protocols already in place?
   - Are there clinical outcomes associated with specific treatment regimens within the diseased population?
   - Are there complementary therapies that can enhance current treatments?

This also gives the sponsor flexibility in tracking their own product update versus other treatment options, all within the construct of the disease-specific registry.

Key factors for increased disease-specific registry engagement

Outreach to rare disease patient populations via a third-party can help ensure all patients feel included and encouraged to participate in the registry. Key initiatives that have proven successful include:

1. Developing direct-to-patient communications, with limited sponsor reference, to highlight the value of participating in the registry that is impartial to current treatment regimen, and emphasize the importance of the registry in promoting disease awareness and overall treatment improvement that is unbiased by currently approved product(s)
2. Coordinating with advocacy groups and disseminating further education about the rare disease, other/alternative treatment options, published data that may not be accessible to the general population, and promoting community events to engage patients in the advocacy activities

As noted in the recent FDA Guidance,[2] it is important to engage with key stakeholders, including patients, caregivers, and advocates, as their engagement can provide different perspectives and experiences to the registry. More patients are becoming empowered and involved with their own treatment regimen and educating themselves on treatment options.[3] Additionally, patients may look to patient advocacy initiatives[4] to further their own treatment regimen and better understand the treatment landscape. Therefore, it is imperative for rare disease registries to focus on operational efficiencies and successes experienced by other rare disease registries.

Importance of Patient Centricity

Recent implementation of rare disease registries has presented anecdotal evidence associated with geographical regions.

- **North America and Europe** – patients look for the opportunity to independently opt-in to clinical research, autonomous from their clinician
- **Latin American and Asia Pacific** – patients rely upon their clinician's recommendation to participate in clinical research

This trend may be due to several reasons, including cultural norms regarding clinical research; levels of exposure to observational, non-interventional registries in these regions; and, personal levels of comfort in disclosing medical information to an electronic database.

Outlined below are some key considerations that can be beneficial when identifying and approaching potential registry patients for either treatment-specific or disease-specific registry designs.

Create a Network/Community

- There has been an increase in patient advocacy, such as the National Organization for Rare Diseases (NORD) and other similar resources, and rare disease registries can find much success when partnering with patient and caregiver advocacy groups. This can help legitimize the research initiative, as well as provide a sense of comfort for the patient and caregiver in feeling that their peers are also included.
- Investment in key marketing and branding efforts can further this development of a "virtual community" and "network."

Share More Data

- Sharing data results of the registry with the enrolled patient population and helping patients to better understand how their peers are responding to similar treatment helps patients to feel engaged and empowered in managing their own care.

Utilize Technology

- As technology embeds itself more and more into our day-to-day activities, there has also been increased use of technology in successfully launching registries. Initial patient screening, encouragement of self-enrollment, reduced burden of data collection, and streamlined user interface for information sharing – these all have a benefit in further extending the engagement reach to rare disease patients.
- Third-party, database vendors with the ability to pre-screen patients based upon Electronic Medical Record (EMR) data and then "invite" patients, via an opt-in portal, have also helped to further the screening/enrollment outreach and improve registry data results.

Registries provide an abundance of real-world insight into rare diseases, the populations who are afflicted by them, and the newly approved therapies that treat them. The data gathered through these studies can help guide research objectives and direction, identify future real-world patient studies, and help build the foundation for strong value story development to help optimize the chance of market access. While there are inherent challenges in designing and operationalizing any registry, those designed for rare diseases present additional challenges in patient identification, engagement, and recruitment. Success comes with overcoming these challenges through a multi-faceted approach that uses proven best practices, innovative solutions, and evolving resources. ■

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REFERENCES

1. See Public Law 97-414, 96 Stat. 2049 et seq. (1983) as amended by Public Law 98-551, 98 Stat. 2815, 2817 (1984), which added a numeric prevalence threshold to the definition of rare diseases. The ODA also defines a rare disease as any disease or condition that "affects more than 200,000 in the United States and for which there is no reasonable expectation that the cost of developing and making available in the United States a drug for such disease or condition will be recovered from sales in the United States of such drug." Section 526(a)(2)(B) of the Federal Food, Drug, and Cosmetic Act (21 U.S.C. 360bb(a)(2)(B)).
2. US Food and Drug Administration. Rare Diseases: Common Issues in Drug Development Guidance for Industry. January 2019 (Revised February 2019). Available at: https://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM629579.pdf. Accessed February 28, 2019.
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