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Patient Engagement and Real-World Data Drive Innovation in Orphan Disease Drug Development

An estimated one in 10 people are affected by a rare disease, and the cumulative economic burden of rare diseases surpasses that of common conditions like cancer or diabetes. Yet of the 7,000 known rare diseases, approximately 95% lack effective treatments. Rare disease research is complicated by small and dispersed patient populations and often limited understanding of disease pathogenesis and progression. These realities create a range of challenges for drug development, including patient identification, endpoint selection, and trial design. However, the orphan disease landscape also offers compelling opportunities to explore innovative patient partnerships and uses of real-world data (RWD) to accelerate medical breakthroughs for individuals with rare disease.

With 350 million people worldwide affected by a rare disease, the collective impact of rare diseases on individuals and society is immense. Innovative technologies including gene therapy and gene editing are bringing effective treatments within reach for many conditions. In 2020, there was a 41% increase in orphan drug designation requests to the FDA from 2019, and 58% of approved drugs were orphan-designated products. While sponsors face many challenges in the orphan drug space, there has never been a better time to partner with the rare disease community to develop novel therapeutics. In particular, real-world data (RWD) is a powerful tool to assist drug developers in bringing better treatments to rare disease patients and families.

Challenges in Orphan Drug Development

Small, dispersed patient populations and a lack of adequate data often go hand-in-hand in orphan drug development. Small patient numbers can make recruiting for site-based natural history studies and clinical trials challenging, limiting the amount of information gathered about disease progression. Even when site-based studies do move forward, the time and travel involved may be prohibitive for some patients, potentially skewing study populations toward participants who have the time and resources necessary to seek care at tertiary care centres and away from those who primarily receive care in the community setting. For example, we analysed health-care facilities visited by 151 participants in our RWD platform with a self-reported diagnosis of one of nine lysosomal storage disorders (LSDs). Fifty-eight percent of these participants did not receive care from a health-care facility we scored as a top-tier centre for LSD care (unpublished results, AllStripes Research). For many of these patients and their families, participating in a site-based study may not be feasible.

Furthermore, in a type of chicken-or-the-egg problem, lack of understanding about rare conditions hinders efforts to identify additional patients. Limited disease characterisation results in a shortage of care hubs and health-care professionals (HCPs) specialising in a given indication. As a result, every patient is following a unique care journey, including how they are diagnosed, what treatment they receive, and the outcomes they experience. These factors make it challenging to predict where patients are being managed and create knowledge gaps in the health care and research communities that ultimately delay diagnosis of new patients. Indeed, a 2020 study from the National Organization for Rare Disorders (NORD) found 28% of patients waited seven or more years for an accurate diagnosis, more than a third were misdiagnosed, and some remain undiagnosed.[1] Half of patients and caregivers surveyed by NORD attribute these delays to a lack of disease awareness among HCPs.

These challenges can also impede clinical trial planning and seeking regulatory approval. Before sponsors can test the efficacy of an experimental therapeutic, they need to understand the condition they are trying to treat and identify meaningful endpoints that will indicate whether their drug is effective. Identifying these endpoints can be challenging in many rare conditions, where no one biomarker, statistic, or measurement may adequately describe a disease's progression or improvement. The nature of rare conditions can further complicate clinical trials since traditional randomised, multi-arm designs may not be feasible for such small, sometimes critically ill populations. Finally, limited understanding of the pathogenesis and progression of rare diseases can make conversations with regulators challenging, as neither sponsors nor regulatory agencies may have a concrete playbook of requirements a drug must meet in order to be approved.

Patients as Partners

For sponsors seeking to tackle the myriad obstacles to orphan drug development, one priority should take precedence over all others: developing a deep partnership with the patient community. In rare diseases, where there may be few or no clinical experts in a condition, patients and caregivers are essential key opinion leaders (KOLs). Successful sponsors will seek to engage with the patient community as the experts they are, soliciting their input in drug programs as early as possible.

The FDA has provided resources to guide sponsors in incorporating the patient community into research planning and decision-making via their Patient-Focused Drug Development (PFDD) initiatives.[2] Given the limited data available in rare disease, PFDD represents an essential part of orphan drug development. Patients, caregivers, and patient advocacy groups each have intimate knowledge of the patient journey, from the path to diagnosis through progression and management. These lived experiences help sponsors understand the true burden of a disease and what a drug must accomplish in order to be considered beneficial by patients and families. Forging community partnerships early on can also benefit both patients and sponsors in the long run by facilitating trial recruitment, retention, and long-term engagement – all of which are essential given the small sample sizes in rare disease. In short, the patient community is a critical research partner for sponsors, and the importance of relationship building and incorporating community feedback into orphan drug programs early and often cannot be overstated.

The Power of RWD for Rare Diseases

With community partnership as the foundation for orphan drug programs, sponsors should also invest in RWD to address the challenges in rare disease research. The power of RWD, or data generated outside a clinical trial, has been discussed extensively in common indications like cancer and cardiovascular disease,

and the paucity of data in orphan diseases creates an even more compelling opportunity for sponsors to invest in robust RWD solutions. The richest source of RWD in rare disease is patient medical records. Embedded in each patient's chart is an in-depth history of their condition, from initial symptoms to diagnosis to current management. Integration of medical record data with other RWD sources can also enhance sponsor understanding of rare disease. Insurance claims can be used to analyse patterns of patient care, including which specialists and facilities patients visit and the costs of diagnosis and treatment. Wearable devices can capture biometric data like heart rate or sleep patterns, providing real-time information on patients' symptoms and progression. Patient surveys or patient-reported outcome measures can interrogate topics like quality of life that would be nearly impossible to measure without directly engaging the rare disease community. Each of these sources of RWD illuminates a unique aspect of the rare disease patient journey and can help build a comprehensive understanding of a condition, even in spite of the obstacles to orphan drug development described above.

Robust RWD can help sponsors overcome challenges inherent in each stage of the orphan drug development process. When coupled with patient surveys, medical record data about symptoms and progression can provide in-depth insights into a condition's natural history, filling gaps in the existing literature. These disease insights can power the development of real-world endpoints for future clinical trials. Natural history data can also yield a detailed picture of the patient journey through the health-care system, especially when coupled with claims data, enabling HCP identification and outreach. Post-approval, medical affairs and commercial teams benefit from a comprehensive map of the patient journey as they strive to educate HCPs about the condition to improve diagnosis rates and ensure patients have access to these new treatments. Finally, detailed knowledge of a condition's natural history can also assist sponsors in educating regulatory agencies, who are less likely to have familiarity with rare diseases than more common indications.

RWD also represents an invaluable resource for clinical trial planning and preparing for regulatory discussions. One of the most frequently cited challenges in orphan drug development is clinical trial recruitment. Successful recruitment starts with site selection, a challenging task when the geographic distribution of patients is unknown, and no centres of excellence exist. Claims and medical record data can help identify where patients receive care and which sites may be most convenient for prospective trial participants. RWD can also assist sponsors in designing clinical trials to meet the unique needs of the rare disease community. As noted previously, traditional placebo-controlled studies may not be feasible or ethical in orphan indications. The FDA has provided a framework for the use of RWD and RWE in non-traditional study designs that help address these challenges. For example, in an "adequate and well-controlled study," historical RWD may be used as an external control arm in place of a traditional placebo cohort.[3] While acknowledging the limitations to using RWD in such single-arm trials, the FDA has also shown willingness to consider these types of trials in regulatory decisions, for example, in the approval of Novartis's SMA gene therapy, Zolgensma. Such flexible trial designs can help not only mitigate the challenges of small populations but also allow more patients to access potential treatments earlier. Finally, RWD can be used for post-approval monitoring. The FDA has indicated that approved gene therapies will likely require long-term follow-up periods given the possibility of delayed adverse events.[4] Investing in RWD solutions early on can help sponsors build toward long-term success of their programs and ensure they can follow gene therapy recipients over time without overburdening patients and families.

Incorporating RWD into orphan drug development efforts offers compelling benefits to patients as well. One of the most widespread uses of RWD is health economics and outcomes research to support payer conversations and ensure patients can access treatments. RWD can also be used to generate evidence that early intervention improves outcomes, providing support for adding appropriate conditions to newborn screening (NBS) panels. NBS in turn can shorten families' pathways to diagnosis, support, resources, and intervention. Additionally, RWD can facilitate patient stratification by disease course or other factors, which can be used to provide anticipatory guidance to patients and families. Finally, use of RWD reduces the burden of patient participation in research. While prospective, site-based studies require substantial travel or time commitments, many sources of RWD already exist or can be collected remotely. With small patient populations, every data point counts, and effective incorporation of high-quality, reusable RWD can help prevent patients and families from becoming overburdened by requests. These examples illustrate ways in which RWD can help sponsors provide tangible benefits to patients beyond the development of an effective therapeutic.

Developing a RWD Ecosystem

The tremendous promise of RWD for use in orphan drug development does not come without challenges. Like all types of data, each RWD source is best suited for specific applications and has specific limitations. In order to maximise the value of data from medical records in particular, sponsors should prioritise RWD solutions that capture high-quality data across the complete patient journey. The reality of medical record data is that a patient's clinical story is captured across multiple care facilities and electronic health records, and interoperability of clinical information remains a challenge globally but particularly in countries like the United States that lack a national health-care system. In rare diseases, this fragmentation is all the more disruptive as patients are often seen at multiple academic and community institutions. To ensure datasets derived from medical records are as complete as possible, sponsors and research organisations should consider several data-quality parameters:

1. **Time period:** Are data available across the patient's journey (from pre-diagnosis to present day), without any significant time gaps?
2. **Comprehensive care map:** Are data from all of the patient's known care facilities available, across tertiary care and community centres?
3. **Diagnostic data:** Are deep data from the diagnostic period available? These notes are likely to contain a wealth of information related to disease onset and progression.
4. **Specialty data:** Are data from critical specialty types available (for example, neurology notes for an epilepsy condition)?

In addition to evaluating the completeness of the medical record dataset, sponsors and researchers should also consider how best to structure clinical information from medical records, to enable comparisons across patients and rare diseases. As noted, one of the reasons medical records are such a rich source of data in rare disease is that clinical notes contain details about the patient's journey and progression that cannot be found elsewhere. However, these notes are unstructured and not recorded in a standard manner across institutions. Furthermore, as so little is known about many rare diseases, it is not always clear what clinical information should be structured for analysis. While data collection standards do exist in clinical research – CDISC and NINDS standards are excellent starting points – the reality is that no gold standard currently exists for how to structure complex clinical data from medical records in rare diseases.

How can we best overcome the challenges inherent in using RWD and achieve their full promise for orphan drug development? The clearest path to achieving this goal in the coming years is through development of a robust RWD ecosystem that incorporates input from all rare disease stakeholders and integrates across RWD types. For example, sponsors will find that patients are the best partners in helping ensure completeness of medical record datasets over time, because they know best where and by whom they have been treated. As such, sponsors should invest in RWD platforms that bring the patient to the table; help build strong, ongoing relationships; and facilitate longitudinal patient follow-up. Additionally, sponsors will see the greatest success in their RWD efforts when they invest early in a RWD strategy that marries disparate data types, complementing weaknesses or gaps in one dataset with information from another. For instance, while claims data can be useful in analysing patterns of patient care, not all rare conditions have ICD-10 codes. Linking claims data with clinical data from medical records can help mitigate this limitation, enhancing overall understanding of care patterns. Likewise, quality-of-life data are critical for understanding disease progression but are rarely captured in medical records; it is therefore essential that patient survey data be integrated with the clinical story. Finally, given the breadth of endpoints and data elements of interest in rare disease, establishing standards for RWD capture will require collaboration among all stakeholders in the rare disease community. Robust data standards, in combination with flexible, iterative approaches to data capture and study design, will allow investigators to compare findings within and across rare diseases. Successful sponsors will invest in infrastructure and solutions that incorporate patient input and facilitate the collection, standardisation, and analysis of the full suite of RWD to generate evidence that advances their clinical programs.

Rare Disease as the Future of Drug Development

Recent advances in clinical care and therapeutic development are creating a future where all diseases will one day be considered rare. The increasing use of technologies like genomic profiling and artificial intelligence allow for patient stratification at a level of granularity never before possible. Likewise, advances in gene therapy and gene editing technologies are helping sponsors develop targeted therapeutics for specific subpopulations. With the drug development landscape moving away from one-size-fits-all therapies for large indications and toward bespoke therapies for smaller and smaller subsets of indications, investing in rare disease makes clear practical sense for sponsors. Some may be intimidated by the many challenges facing drug developers in the orphan disease space. Yet today holds tremendous opportunity to set new standards for involving the rare disease patient community and using RWD to fill critical knowledge gaps. By embracing this unique moment, sponsors can take part not only in developing more effective treatments for critically underserved populations but also in defining a new playbook for the drug development industry as a whole.

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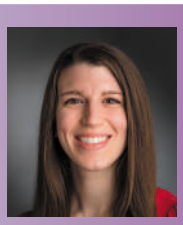

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