Confronting the Challenges of Rare Disease:

SOLUTIONS ACROSS THE ENTIRE PRODUCT LIFE CYCLE

The Orphan Drug Act of 1983 brought increased awareness to the need for new treatments for rare disease patients and provided incentives to pharmaceutical manufacturers of orphan treatments, including tax credits for the costs of clinical research, seven years of patent exclusivity, and the waiver of Prescription Drug User Fee Act (PDUFA) filing fees. Of the 3,500 drug designations issued by the Office of Orphan Products Development since 1983, more than 500 have resulted in marketing approval.[1] Still, only 5 percent of the estimated 7,000 known rare diseases have a therapy approved by the U.S. Food and Drug Administration (FDA), leaving substantial unmet medical needs for patients.[2]

Challenges to clinical development and commercialization of orphan drugs are many. Although these challenges may be similar to non-orphan drug development and marketing, the solutions are often different in the context of a rare disease with which there is often little medical experience. The issues are also more acute with increasing rarity of the disorder. This paper is intended as a discussion of the commonly encountered hurdles in studying rare diseases and how a cohesive and holistic approach can mitigate issues and help bring new treatments to patients.

Clinical Trial Design Requires Understanding First

A rare disease is usually a lifelong journey for the patient. Diagnosis may take place before 18 years of age, and, in some cases, in the first year of life. By their very nature, these diseases pose a significant challenge to patients, caregivers, and healthcare providers.

For a clinical trial, the pool of potential patients is very small and often geographically dispersed — both factors create unique challenges to sponsors seeking to recruit these patients. Moreover, the standard of care may vary widely among patients, institutions, and countries.

Sponsors can prepare for some of the challenges by understanding the natural history of the rare disease. Epidemiologic data on disease frequency, disease progression, and patient outcomes, are vital to understanding the size of the target patient population, clinical trial feasibility, and benefit-risk issues.

This may be done by partnering with existing disease registries or patient cohorts maintained by individual investigators. However, accessing and analyzing this evidence to support informed decision making in rare disease research can often be quite challenging and a sponsor may elect to establish their own disease registry. A natural history registry provides sponsors with the information to define the disease population and disease subtypes (important for clinical trial eligibility

criteria), understand other critical clinical study design elements, select appropriate outcome measures, develop or optimize biomarkers, and understand the burden of illness and quality of life of patients.

The current emphasis on "real world evidence" (RWE) from registries or electronic medical records or claims databases and the willingness of regulators to accept data from sources other than traditional randomized clinical trials can have a positive impact on the development of treatments for rare diseases. The 21st Century Cures Act, enacted into law in December 2016, was implemented to speed the FDA drug and medical device approval process to include data from the "real-world" setting. If conducted properly, the control arm of a clinical trial could come from RWE. Although these types of protocol-driven studies were conducted in the past, they are now becoming more widely accepted, provided the design is robust and appropriate methods are applied to analyze and interpret the data.

Incorporating patient-reported outcomes into RWE studies is critical. Endpoints that reflect medically significant change can be debatable in rare diseases; small improvements in quality of life are often sought rather than a cure. These outcomes should be negotiated while working closely with key opinion leaders and regulatory agencies in design of the clinical program.

Engaging Patients in a Trusting Relationship

When patients with a rare disease enroll in a clinical trial, they often do so because there are no or limited usual care options. Unlike the case with most clinical trials, site identification and patient recruitment for a clinical trial of a rare disease treatment may begin by first identifying patients and, through them, their treating physicians. In many cases, a physician may be treating only one or two patients with a rare disease, which is a different paradigm for site engagement. In terms of data collection, the clinical trial may include direct-to-patient or in-home collection of biologic specimens and data collection by a clinical trial nurse.

In light of the particular importance of identifying as many patients with the rare disease as possible in a natural history registry and in a clinical trial, engaging patients early and often in the drug development process is vital. Developing close ties with patient support groups and using social media are excellent strategies to reach out to patients.

PATIENT ADVOCACY GROUPS

Patient advocacy groups are experts on the impact the disease has upon the patient and their caregivers. These groups often start as grass-roots organizations, formed out of pure desperation and a lack of information. Resourceful by nature, these communities assemble their information from whatever sources are available to them, which in some cases may be primarily from the patients themselves. They are an excellent source of information on the disease and patient needs, and they can be fierce in their determination to fight for the ideas, goals, and vision of their community.

A wide range of stakeholders, including the sponsor, physicians, payers, government officials, and service providers, have a huge opportunity to build trust and align common goals with the rare disease patient community by working closely with patient advocacy groups. To do so, advocacy groups should be consulted early in the development process. When trusting relationships are fostered with advocacy organizations, they can be invaluable to help form a liaison between sponsors, researchers, providers, patients and other key players to enable patient identification, improve disease awareness, discuss study design, establish patient-important outcomes and, above all, foster a sense of community.

SOCIAL MEDIA TOOLS

Challenged with few sources of information about their condition, patients with a rare disease are especially active on social media, using it to reach out to patients with the same or similar conditions or to educate others about their disease. By posting on Facebook and other social media, patients and advocacy groups spread awareness of rare or orphan diseases, and, in the process, can help build an understanding of the disease, create or strengthen the patient community, or find medical experts.

Savvy sponsors understand an appropriate social media strategy can help them reach rare disease patients at very little cost. Such a strategy may include tactics to better inform clinical trial design, pre-identify patients for a clinical trial, and offer support during the period when a product is under regulatory review. Social listening can also provide valuable information about a specific indication and population. When done sensitively, this can provide sponsors direct access to rare disease patients that they otherwise never would have had.

Expanded Access Program Considerations in Rare Disease Populations

Given the small numbers of patients on which an NDA, BLA or MAA may be based, additional data collection may be warranted at the end of a clinical trial. This might involve rolling over patients into an observational study at the end of a clinical trial or enrolling them into an expanded access program (EAP). The proper long-term monitoring of these patients, with collection of key variables in alignment with a clinical trial, the analysis of resulting data, and registry setup in a post-approval scenario, should be considered a part of the development strategy.

Expanded Access Programs provide an avenue for patients with serious or life threatening illnesses and limited treatment options to obtain access to investigational drugs outside of a clinical trial. Manufacturers implement expanded access programs to provide a potential avenue of access to unapproved therapies for patients that do not have the option of participating in a clinical trial due to ineligibility and / or closure of the enrollment period for the clinical trials being conducted to support the marketing application. Given that rare diseases are often associated with few treatment options, the conduct of an EAP in these settings may be more likely as the rare disease drug candidate approaches potential approval.

Selecting the optimal EAP design is an important consideration, particularly in the rare disease setting. The single patient IND EAP design should be considered if geographic concentrations of patients do not warrant a “site driven” model. Alternatively, in rare disease settings where it is typical for significant numbers of patients to converge around specialized treatment centers for chronic and long term treatment, the large population / treatment protocol EAP model might be more appropriate and efficient.

Data collection in the EAP is a domain that also warrants special consideration in the rare disease setting. EAPs typically limit data collection to drug accountability, usual care procedures, and safety data. In scenarios where patients are traveling significant distances to specialized treatment centers, as is often the case for specialized care of a patient with a rare disease, challenges relative to data collection can occur if these activities are not conducted within the framework of visits to the center of excellence. Creativity relative to obtaining information from a source more local to the patient may be needed.

Finally, during the planning of an EAP, it is also important to ensure the continuum of care — that there is a plan for transitioning patients over to the commercial setting once the product is approved, which includes navigating the payer landscape. This can be particularly important in a rare disease where unique reimbursement and supply chain considerations exist.

PAYER DATA

Creating a brand name and leveraging it for payer coverage can be a big hurdle. Generating and monitoring payer data can be a great marketing tool for the product/brand.

It is critical to have a current and broad understanding of the payer data associated with each rare condition and treatment. Prescribers need to know that payer coverage is attainable. Having details on current policy and coverage guidelines promotes a positive expectation for the prescriber and the patient. This information can be used to create marketing tools or sales messaging around coverage and also to create pressure for other payers to publish coverage rules and/or amend previously unfavorable coverage policies.

Into the Marketplace: Meeting Patients & Prescribers During & After the Clinical Trial

Specialized services provided directly to patients and prescribers are essential to marketing treatments for rare diseases. For example, reimbursement services and funding assistance are critical to ensure long-term treatment adherence. Field-based clinical educators and reimbursement specialists allow sponsors to bring reimbursement and clinical services directly to prescribers and patients. Team members must be skilled in providing patient and prescriber education and training and in collaborating alongside pharmaceutical sales and brand teams.

A best practice is to create patient ambassadors who serve as points of contact for patients as they navigate their journey. They act as liaisons among all stakeholders — sponsor, prescriber, pharmacy, patient support provider, and payer — to ensure timely access to treatment and care. For example, transitioning from a clinical trial to a commercially available product may mean a new care team, which can add complications to a patient's life, especially when the new staff members aren't familiar with the new treatment.

By deploying clinical nurse educators in the field, sponsors can help create a positive impact on the patient journey and brand experience by engaging prescribers and empowering patients. Collaborating with the product's sales teams, these nurse educators instruct patients and prescribers about the disease itself, the clinical benefits of the product, and the support services available to patients and their families.

By using both office and field-based nurses, the sponsor can provide a variety of telephonic and in-person support for prescribers and patients. These clinicians assist with product and program education along with patient training and advocacy. They become a part of the rare disease patient care team and bridge a variety of services.

REIMBURSEMENT AND PATIENT ACCESS SUPPORT

Added to the complexities of the disease is the challenge of verifying insurance coverage for treatment once the product is approved, particularly when there are vague payer policies and coverage details for rare treatments.

Reimbursement hubs can alleviate much of this burden by acting as an extension of the prescriber practice and investigating all payment options available. Staffed by qualified specialists, the hub leverages indepth knowledge of the medication and the reimbursement landscape to focus on securing patient coverage for the treatment. Such a team should engage a variety of payer systems and networks and work on behalf of the prescriber and the patient to educate payers on the treatment and provide clinical documentation to support coverage. Not only does this patient-specific approach ensure timely submission of information and followup, the hubs can work beyond current policy guidelines to advocate for coverage through appeals and escalate non-coverage issues to top levels within payer organizations.

Like field-based nurses, field-based reimbursement specialists can work directly with physicians and their office staff, helping to alleviate administrative burdens and reimbursement frustrations.

Field and hub teams quickly learn utilization management and prior authorization requirements for regional and national payers and proactively educate prescribers and patients on these requirements. This avoids unnecessary delays to treatment as well as prior authorization denials by payers.

These teams also benefit the manufacturer of the treatment. They usually share changes in prior authorization requirements or coverage with the manufacturer's account team — promoting a multifaceted approach to address restrictions in policies and working to ensure an expedited process for contacting payers.

Finally, by sharing findings regarding payer coverage or exclusions with brand leaders and representatives, these teams are also supporting the rare disease community. When the prevalence of the disease is low, there is an increased need to share these details on each case. Every approved case is a victory for the rare disease community and a milestone that can further influence future coverage.

Conclusion

Patients with rare diseases and their caregivers have unique challenges. Confronting these challenges requires a comprehensive approach that benefits the patients and their caregivers and health care providers. By looking holistically at the life cycle, beginning with an understanding of the dynamics of the disease, continuing through recruitment into clinical trials and expanded access programs, through product availability after approval, sponsors can facilitate the drug development and commercialization process for treatment of rare and orphan diseases.

REFERENCES

1. Office of Orphan Products Development, Narrative By Activity. 2017

2. “Rare Diseases and Orphan Products: Accelerating Research and Development” Committee on Accelerating Rare Disease Research and Orphan Product Development Board on Health Sciences Policy.

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