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Challenges and strategies for rare diseases trials

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For most patients with rare diseases, finally receiving a diagnosis is a major milestone, but a dearth of proven treatment opportunities often leaves their prognosis unchanged. Approved drugs are available for just 5% of the approximately 7,000 rare diseases identified so far, many of which are life-threatening or life-limiting. The pharmaceutical industry is making inroads through R&D despite the unique challenges facing clinical trials for rare diseases, often navigating without regulatory precedents and with an uncertain commercial outlook. Progress can therefore feel slow in spite of the priority that many drug companies place on these patients and their unmet needs.

Clinical Trial Landscape:

Individually, rare diseases are so-called because of the low number of prevalent patients, with long-standing definitions being fewer than 200,000 people in the US and fewer than 1 in 2,000 people in the EU. However, they have a large collective footprint and their combined burden is vast. According to Orphanet, there are an estimated 300 million patients with a rare disease, equivalent to around 4% of the world's population. As such, there is a huge opportunity to evaluate new treatments in these patients within clinical trials.

According to a recent industry report by Pharma Intelligence on rare disease trial strategies, industry trial activity is strong and has consistently grown through the last decade, achieving a minimum of 5% growth every year between 2013 and 2019. In 2010, the biopharmaceutical industry initiated 884 rare disease studies, with the total expanding year-on-year to a peak of 1,609 in 2019. Although there was a slight 4% contraction in the pandemic-affected 2020, the overall trend is clearly positive and activity through 2021 has been robust. This growth has come from both the oncology and non-oncology rare disease segments. The proportion of oncology studies has remained consistently at 60–65% of the total, indicating the attention on both traditional rare diseases as well as oncology opportunities.

Currently, very few rare disease clinical trials are taking place in India. The country is among the top 30 locations, although considering its large population of patients that suffer from rare diseases, India is underrepresented in clinical research. Less than 3% of rare diseases clinical trials include investigational sites in India, which is much lower than the figures for prevalent chronic diseases such as diabetes (6%) or hypertension (8%). This therefore poses an opportunity for clinical trial sponsors seeking to recruit patients outside of the typical hotspots such as the US and Western Europe.

Key Challenges for Rare Diseases Clinical Trials

- **Studies for rare diseases typically take longer to recruit and conduct:** Owing to the initial challenge of diagnosing rare diseases, it is unsurprising that clinical trials for these patients typically enroll at a slower rate. This is most pronounced for non-oncology rare diseases, where a clinical site enrolls a median of 0.68 patients per month, which is three times slower than the average across all non-oncology diseases (2.02 patients/site/month). As a consequence, the enrollment duration of rare disease trials is typically longer, which adds to the cost burden of rare disease R&D.
- **Patient scarcity adds to study costs:** Traditional clinical research remains heavily centralized around the investigational site. To compensate for the sparse eligible patient numbers and slow enrollment benchmarks for rare diseases, clinical trials either require a larger number of clinical sites, or simply recruit fewer participants. A larger number of sites adds additional complexity, burden, and cost to each study, while conversely smaller sample sizes limit the statistical strength of the results. Rare disease drug developers are therefore prioritizing keeping R&D costs down, supported by greater flexibility at the regulatory review stage.
- **Being unable to source relevant trials typically prevents participation:** For patients with rare diseases, the difficulty in locating relevant trials that are an appropriate match to both geographical location and/or condition is a challenge. Even when trials are available, sponsors must overcome a lack of awareness among physicians and patients.

Strategic Recommendation

From rare disease clinical trial benchmarking and patient insights into the clinical trial process, Pharma Intelligence can make a series of strategic recommendations for sponsors of rare disease clinical research. These include gathering insights from clinical experts to design patient-centric studies, building trial awareness among important physician and healthcare professional (HCP) groups, and leveraging advocacy groups to speed up patient recruitment. This ultimately will allow sponsors to gain a competitive edge in their rare disease trial strategies.

- **Gather insights from clinical experts to design patient-centric studies:** An industry survey with Rare Patient Voice shows the essential role of physicians in rare disease clinical research. Physician referral is by far and away the most common route to study participation, while physicians also are a common source for trial awareness and information. Physicians can also play a pivotal role in the trial design process, being much closer to the disease in question and patients' unmet needs. With rare diseases in particular, there is comparatively little information on traditional inputs that inform study design, such as patient availability, treatment practices, and clinical endpoints. Thus, HCP outreach and engagement are crucial to access these insights, which in turn facilitate the planning and execution of successful clinical trials.
- **Build trial awareness among key stakeholders from the outset:** Recognizing the growing influence of patient organizations and disease advocacy groups, particularly within the rare disease universe, any trial awareness strategy also needs a patient-focused component. This can be as simple as developing patient-friendly materials and a website presence. Advocacy group websites are the number one resource for patients who have not yet enrolled in a trial, second to general internet searching, as revealed by a recent survey. Trial awareness among patients, whether direct or through support networks, is central to any successful rare disease trial as it begins enrolling.
- **Embrace new end-to-end recruitment models:** Lastly, an innovative patient recruitment model is particularly

relevant for rare disease studies, owing to the disparate geographic spread of patients and importance of advocacy groups. The patient recruitment collective can bring together a diverse range of patient-facing organizations from traditional recruitment partners through to disease awareness organizations, patient advocacy groups, pharmacies, and even diagnostic service providers. By creating and tapping into a network of validated partners that can steer patients in the direction of clinical trials, study sponsors can cast the net far wider and more equitably.

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