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Drug Development for Rare Diseases

Edited by

Bo Yang
Yang Song
Yijie Zhou

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Drug Development for Rare Diseases

A disease is defined as rare if the prevalence is fewer than 200,000 in the United States. It is estimated that there are more than 7,000 rare diseases, which collectively affect 30 million Americans or 10% of the US population. This diverse and complex disease area poses challenges for patients, caregivers, regulators, drug developers, and other stakeholders. This book is proposed to give an overview of the common issues facing rare disease drug developers, summarize challenges specific to clinical development in small populations, discuss drug development strategies in the evolving regulatory environment, explain generation and utilization of different data and evidence inside and beyond clinical trials, and use recent examples to demonstrate these challenges and the development strategies that respond to the challenges.

Key Features:

- Rare disease.
- Drug development.
- Innovative clinical trial design.
- Regulatory approval.
- Real-world evidence.

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Introduction to Rare Disease Therapy Development

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1.1 Introduction

Plus ça change
Plus ç'est la même chose
(The more that things change
The more they stay the same)

~ Jean-Baptiste Alphonse Karr (1808–1890)

The circumstance of medicine for rare diseases has been described as both rapidly developing and unchanging. Both descriptions have merit. There are approximately 7,000 known rare diseases (Haendel et al., 2020; National Institutes of Health, 2020), and certain commonalities emerge. Many of these rare diseases are genetic in origin, with 80% thought to have an identified genetic cause, resulting in most (50%~75%) of the patients being children (Wright et al., 2018). There is no explicit international definition of a serious disease, but typically, many rare diseases are quite severe, even life-threatening or life-shortening, in nature. Therefore, a clinical

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expectation of a gradual patient decline (with varying timeframe) is anticipated. Therapeutic progress has been dramatic (Miller et al., 2021), with exciting principles established, in selected areas such as chronic myeloid leukemia, spinal muscular atrophy, and cystic fibrosis. For example, the 5-year survival rate for chronic myeloid leukemia, previously about 30%, has been cited as at least 89% since the advent of imatinib therapy targeting the genetic source of the disorder, the BCR-ABL1 gene, in 2001 (Pray, 2008). Yet, product approvals are non-existent for more than 95% of rare diseases (Kaufmann et al., 2018), frequently necessitating decades-old therapeutic paradigms that appear more suitable for a discussion of history, not modern science. Huntington's disease serves as a sobering example. When George Huntington, recently graduated from Columbia Medical School, published in 1872 (Huntington, 1872) on the disease eventually named after him, it generated more interest, even in his day, than afforded most rare diseases. He was in touch with some eminent clinicians of the day and expressed hope that science would one day provide answers; yet, 150 years after Huntington's seminal account, while the genetic cause has been isolated, and medications can reduce choreic movement and ease psychiatric symptoms, the treatment summary provided online by the Mayo Clinic begins with a blunt assessment, "No treatments can alter the course of Huntington's disease" (Mayo Clinic, 2020). Over the past century and a half, the circumstances have changed yet fundamentally stayed the same.

1.2 Definitions

The notion of rare disease has been defined variously across geographies. Perhaps most cited is from the Orphan Drug Act passed by the US congress in 1983, leading the Food and Drug Administration (FDA) to label a disease as rare if it affects fewer than 200,000 people in the United States (FDA, 2020). In the European Union, as stated by the European Medicines Agency, a disease is defined as rare if it affects fewer than five in 10,000 people across the European Union (European Medicines Agency, 2018). In Japan, according to the Ministry of Health, Labour and Welfare, such diseases are defined as those affecting fewer than 50,000 people, or one in 2,500 people (Hayashi and Umeda, 2008; Ministry of Health, Labour and Welfare, 2009). Globally, the World Health Organization uses a prevalence of 0.065%–0.1%. It is commonly estimated that around 10% of the global population suffers from a rare disease, with around 250 new such diseases identified each year (Dawkins et al., 2018), although these obviously vary by the definition applied. Hence, while being individually rare, the currently identified rare diseases are collectively not rare at the population level (Griggs et al., 2009).

1.3 Differences in Clinical Setting for Rare Diseases

As development of therapies inevitably follows clinical understanding, we should first consider a few differences in the clinical understanding of rare diseases.

1.3.1 Understanding of the Disease

Clinical understanding of the disease can frequently be uncertain, and it is possible that little to no research has been conducted previously, especially in disease subtypes. The underlying cause of the disease may or may not be known. Treatment guidance documents may be out of date or non-existent (Stoller, 2018). Identification of key prognostic factors may be difficult to identify yet particularly important to incorporate into the design (e.g. as stratification factors) of small studies, which are prone to imbalance and bias. The number of clinicians (and hence program development leads) with experience in the area will likely be limited, prompting more "on-the-job" learning for the development team. How best to measure disease progression or remission may also be unclear, which creates uncertainty as to the best endpoints to use in a clinical trial. FDA guidance on rare disease drug development (FDA, 2019) indicates that "For many rare diseases, well-characterized efficacy endpoints appropriate for the disease are not available."

1.3.2 Identification and Diagnosis of Patients

Patients with rare diseases often endure years of symptoms before gaining a diagnosis. In the case of children, the average is 6–8 years before a diagnosis is obtained (World Economic Forum, 2020). Over 40% of patients obtain an incorrect diagnosis more than once. As a result, the patients can be difficult to identify, particularly in commercial databases, such as insurance claims databases. Also, the patients can finally present at study screening in widely varying states of disease. A 2019 survey from Tufts University (Burton et al., 2021; Tufts Center for the Study of Drug Development, 2019) found that approximately 81% of screened patients were ineligible to enroll and 56% failed to be randomized in rare disease clinical trials, versus 57% and 36% of patients who fell into the categories in non-rare disease trials. Even once identified and enrolled, retention may suffer if desperate patients discontinue to try other, even off-label, therapies.

1.3.3 Funding Challenges

It only makes sense that a disease which has fewer patients will have a lower potential for revenues. As a result, many rare disease researchers struggle at the outset to obtain funding in pursuit of therapies. To compensate, the standards for clinical benefit (and price) may need to be altered to justify the up-front investment risk.

For fiscal year 2019, the National Institutes of Health was appropriated $39 billion, of which only $38 million (0.1%) was awarded to study a wide range of rare diseases (Zhu et al., 2021). However, there have been efforts to increase funding for rare diseases. In October of 2021, the FDA announced 11 new congressionally funded clinical trial research grants, awarded by FDA's Orphan Products Grants Program, which sums to more than $25 million of funding for rare diseases over 4 years (FDA, 2021).

1.3.4 Regulatory Uncertainties

A lack of clear precedents, as is usually the case, can leave sponsors uncertain how any particular development scenarios or choices will be received. Standards, such as orphan drug designation (discussed in a later chapter), have been developed to aid in this understanding, but considerable risk and uncertainty remain. This uncertainty extends to the payor domain, often critical in rare diseases in which the patients can generally not be expected to afford cutting-edge therapies on their own. As a result, studies specifically targeting payor requirements across varying geographies may be needed.

1.3.5 Privacy Considerations

Clearly, avoiding identification of specific patients is a greater challenge when there are fewer patients with the condition. As a result, following privacy regulations and reporting practices that reduce this possibility is important in the rare disease space. For example, reporting patients with a specific rare genotype might constitute a small enough group to allow identification based on other information (e.g. country, age, and gender). Generally, no groups smaller than a pre-specified size (e.g. 5) are reported.

1.3.6 Pediatric Focus

Approximately 80% of rare diseases are inherited, and most of those patients are children (Wright et al., 2018). This fact touches on many of the development aspects already mentioned. Recruitment activities (including informed consent) are more complicated due to the need to involve parents/guardians; data collection for some endpoints, such as subjective patient-reported outcomes, may be even less certain; and additional privacy/transparency requirements may apply. Recruitment of pediatric patients in pre-market studies is more widely conducted than in common diseases, which often only enroll patients once a therapy is marketed.

1.4 Scope

In the remainder of this work, we will attempt to give an overview of the clinical development implications of researching new therapies in this area.

The emphasis is on scientific and, in particular, clinical data-driven considerations, and not on issues which are purely operational, manufacturing, legal, or commercial in nature. (While basic research and non-clinical studies are critical to the development of any new therapy and may differ in nature for rare diseases, they are not in the already wide scope we attempt to purview. Neither are the legal/regulatory ramifications associated with privacy concerns.) However, these quantitative issues are addressed in a non-technical way with most technical statistical considerations left to references provided. After some discussion of the developmental implications of the rare disease setting, we will provide clinical case studies of approaches increasingly leveraged therein. We will also provide a summary of the various regulatory designations and options which figure more prominently for rare diseases. A chapter on modeling and simulation approaches to bridge notable data gaps is presented, followed by another approach for additional relevant information, real-world evidence. Last, we look at how these elements come together for the prototypical rare disease patient: the child (Wright et al., 2018). These works are written with the general clinical research audience in mind, hopeful that the collected works herein can shed light on both the rewarding opportunities and the undeniable challenges which coexist in clinical research for rare diseases.

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