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Orphan drugs: major development challenges at the clinical stage

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Biotechnology has provided powerful tools to assist in research and development (R&D) for rare diseases. However, orphan drug development presents several major challenges and obstacles, such as low disease prevalence, disease severity, small and heterogeneous patient populations, difficulties in patient recruitment, and limited knowledge of the natural history of disease, among others. Several strategies can be used to plan for and overcome these clinical and regulatory challenges, namely improved clinical trial design, improved patient recruitment, and closer collaboration with the regulatory authorities and with patient associations. As growth in the orphan drug market is expected over the next few years, improving its relevance in the global pharmaceutical market, further challenges might present themselves in the development of orphan drugs.

Introduction

Biotechnology has provided powerful tools to assist in drug R&D, particularly for rare diseases. However, this group of diseases remains a major unmet need with few treatment options [1–3]. A clear definition of rare diseases is still lacking, because different legislation and policies have been implemented according to country and global region [2]. In the European Union (EU), a rare disease is defined as a disease with a prevalence of not more than five in 10 000 people in the Community [Regulation (EC) No. 141/2000] [4]. Compared with the EU, the USA and WHO define a rare disease based on a higher prevalence of the disease of 6.4 and 6.5–10 in 10 000 inhabitants, respectively [2]. Moreover, a rare disease is defined as a disease or condition that affects fewer than 200 000 individuals in the USA [5–7] and fewer than 50 000 in Japan [8].

Although regulatory and financial incentives have been used to promote orphan drug development [1], the number of therapeutic options for rare diseases remains limited, particularly in certain therapeutic areas, namely bone and connective tissue, ophthalmic, renal, urinary, and reproductive rare diseases [9].

Orphan drug development presents several major challenges and obstacles, such as low disease prevalence, disease severity, small and heterogeneous patient populations, difficulties in patient recruitment, and limited knowledge of the natural history of disease, among others. Several strategies can be used to plan for and overcome these clinical and regulatory challenges, namely improved clinical trial design, improved patient recruitment, and closer collaboration with regulatory authorities and patient associations [10]. Furthermore, recent advances in drug development, namely personalized medicine, provide new avenues to improve research in rare diseases and orphan drug development [11].

In this context, here we explore the challenges during orphan drug development with a particular focus on the clinical stage as well as on strategies available to overcome such challenges.

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Challenges and strategies to overcome them

Clinical research in rare diseases faces evident challenges and obstacles, such as very or exceptionally low disease prevalence, small and heterogeneous patient populations, difficulty in recruiting such patients, disease severity, lack of or limited knowledge of disease natural history, and high attrition rates during R&D processes [10,12–14]. These challenges can be divided into four major groups (Table 1), related to study design and execution, patient recruitment, regulatory, and others. Here, we further explore such challenges.

Clinical trial design and execution challenges

Notable differences between interventional trials in rare versus nonrare diseases have been reported, particularly regarding patient enrollment, study design, and blinding and randomization procedures [12]. In fact, clinical trials on orphan drugs present several challenges in regard to study design and execution, particularly derived from the lack or incomplete understanding of the natural history of the disease and heterogeneous disease phenotype and clinical course. Thus, a better understanding of the natural history of the disease would improve trial design, particularly in terms of disease-stage stratification [10]. As an example, the development of targeted cancer therapy has benefited from recent developments in the identification of synthetic lethal relationships between rare disorder genes with oncogenes and tumor suppressor genes, providing new therapeutic opportunities [15]. A better understanding of the mechanisms involved has also proven to be a useful tool towards orphan drug development, for example in thyroid-associated ophthalmopathy, the ocular manifestation of Graves' disease [16]. In addition, advances in stem cell research and microfluidics have provided novel microphysiological systems or tissue chips that could be used in rare disease research [17]. In this context, the biobanking of samples from patients with rare diseases might be helpful in advancing such approaches, although adequate resources remain lacking. In addition, clinical trials in patients with lymphangioleiomyomatosis have also benefited from major advances in the understanding of the pathophysiology of this cystic lung disease [18].

Moreover, the identification and definition of clinically relevant outcomes is also dependent on the knowledge of the disease because the choice of study endpoints represents a crucial step in clinical trial design [10].

The global geographical dispersal of patients and researchers in orphan drug trials can limit clinical trial execution, especially because of the need for coordination between numerous clinical study sites and the travel burden for patients. In this context, several trials have implemented novel designs that include at-home measurements or remote data collection [10], as discussed further below.

The lack of prior clinical studies to establish a template for study execution also constitutes a challenge in clinical trial design for orphan drug development [10].

Although these obstacles are not unique to orphan drug trials, their solutions might be more difficult to find in these trials specifically compared with other disease groups.

TABLE 1

Major challenges in orphan drug development

Group	Specific challenges
Clinical trial design and execution	Poor understanding of natural history of disease because of few observational studies studying disease progression Heterogeneous populations with variable phenotypes and clinical courses Lack of clinically relevant endpoint definitions and validations Geographical dispersal of patients and researchers Lack of prior clinical studies to establish template for study execution
Patient recruitment	Small number of patients Low disease awareness Ill-defined therapeutic approach by physicians
Regulatory	Lack of comprehensive evidence Need to meet standard criteria for approval
Others	Reimbursement scrutiny Pediatric trials Ethical concerns

Patient recruitment challenges

Patient recruitment is a major challenge in orphan drug trials. The small number of patients, the low disease awareness in the general population, and the typically ill-defined base of treating by physicians represent specific challenges that must be addressed [10,19,20]. Therefore, typical randomized placebo-controlled clinical trials involving several hundreds of patients might not be feasible in orphan drug development [12,21], particularly when considering the pediatric population.

The small number of patients in orphan drug trials clinical trials presents certain challenges, in particular: (i) limited number of eligible subjects, which impacts study design and the resulting statistics; (ii) higher variability because of the smaller nature of the trial; (iii) impact of missing data is likely to be more crucial, leading to more of an influence on the conclusions; and (d) need for improved data occultation to prevent participant identification [20].

In fact, small patient populations limit study design and implementation and the genetic basis or the co-morbidities associated with many rare diseases might be confounding factors in study reproducibility and predictability [19,20]. Hence, given the need to study disease-modifying agents in patients from early-stage to advanced-stage disease, the definition of inclusion and exclusion criteria based on disease stage or other patient characteristics might be difficult [22].

As previously mentioned, the geographical dispersal of patients and researchers in orphan drug trials can represent an obstacle for clinical trial execution, particularly because of the small number of patients [10]. Therefore, during the design phase of the clinical trial, several aspects should be taken into account, namely: (i) identification of the countries with a sufficient number of suitable study participants; (ii) determining whether these patients are available and are willing to participate; and (iii) identification of centers of excellence with the therapeutic and operational skills to execute the intended trial [23].

Typical patient databases commonly used as a recruitment resource in clinical trials are of limited utility in orphan drug trials, because the inclusion criteria often comprise specific assess-

ments that are not usually recorded on medical charts. Moreover, patient recruitment might also be affected by simultaneous studies of the same rare disease, because the enrollment in a first trial might lead to ineligibility for a second trial [19].

Several strategies can be used to address the challenge of patient recruitment, and are discussed further below.

Regulatory challenges

The regulatory framework and marketing authorization of orphan drug trials has been reviewed previously [1,2]. Despite the marked differences between clinical trial design and execution for rare diseases compared with nonrare diseases, orphan drug trials should use an approach as similar as possible to trials for nonrare diseases, with the highest design standards [12].

Even though there are no major differences in the information required about orphan drug effectiveness in regard to the marketing approval criteria, regulatory authorities such as the US Food and Drug Administration (FDA) have expressed a higher receptivity and flexibility in the approval standards for orphan drugs regarding the evidence base. Furthermore, the European Medicines Agency (EMA) has also provided guidance on criteria and procedures for the granting of marketing authorization under exceptional circumstances, particularly in regard to rare indications in which comprehensive evidence is still not fully available [19]. Hence, close collaboration with regulatory authorities might contribute to an improved and highly individualized path to drug development and registration [24].

Other challenges

Other challenges might be associated with orphan drug development, including ethical concerns and reimbursement scrutiny.

First, the impact on payers is increasing particularly because of the growing number of orphan drugs on the market, potentially leading towards more attention being paid to orphan drug pricing and reimbursement. Thus, a low-cost delivery model must be implemented that enables the delivery of orphan drugs by specialty pharmacies to the relevant patients [22].

Second, most rare diseases affect the pediatric population and half the current orphan drug trials assess innovative medicines, which adds to the previously mentioned challenges in terms of the complexity of trial design, acceptability by regulatory authorities, and ethical considerations [22,25]. In addition, the inherent biological evolution of children accompanied by changes in disease presentation, the physical, intellectual, and psychological growth changes, as well as family dynamics, might also impact patient recruitment, compliance, retention, and management in the context of clinical trials, particularly in regard to orphan drugs [22,23].

Innovative research strategies in orphan drug development

The establishment of incentives (e.g., protocol assistance, long marketing exclusivity, and reduced licensing fees) for clinical research on rare diseases both in the USA and EU has led to a rapidly growing demand for clinical trials in orphan indications [26,27]. Furthermore, public incentives and more expedite processes have made orphan drug development more financially viable [24]. Also, new research methods (e.g., crossover trial design and propensity score matching) have been proposed and/or used to study health and disease outcomes in patients with rare diseases in observational data, because they are already in use for common indications. Hence, the knowledge of these research methods could provide researchers with better tools for study design, execution, and data interpretation in orphan drug trials [28].

Several innovative strategies have been proposed in the context of overcoming the challenges in orphan drug development. Furthermore, these strategies can be divided into two main groups according to the primary aim, namely addressing the small number of patients and outcomes, and promoting patient recruitment and retention, as further detailed in Table 2.

Addressing the small number of patients and outcomes

To this end, several strategies can be used, including: (i) minimizing the number of required participants through improved study design (e.g., factorial design, response-adaptive randomization, or others); (ii) making use of underpowered conventional studies by improved statistical analysis or incorporation into larger evidence context (i.e., a combination of small individual studies might provide definitive evidence on a research question that would not be perceived with classical research methods); (iii) maximizing outcome information either by focusing on high-risk patients who exhibit a higher probability of the outcome or by using more efficient outcomes measures (e.g., continuous, surrogate, or composite endpoints); and (iv) facilitating adjustment for the confounding factors either by improved study design or by using propensity score matching [28].

Other novel methods are available for use in orphan drug development, as recently proposed by the ASTERIX project, namely for extrapolation, sample size re-estimation, dynamic borrowing through power priors, and fallback tests for co-primary endpoints [29]. In addition, model-based approaches, such as nonlinear mixed effects modeling and Bayesian approaches, have emerged as tools for research in rare diseases, such as adrenoleukodystrophy [30,31] and GNE myopathy [32]. Bayesian approaches have also been used by the Innovative Methodology for Small Populations Research (InSPiRe) project to develop a novel decision-making method for small population clinical trials [33]. Several recommendations have also arisen from the Integrated Designs and Analysis of Small Population Clinical Trials (IDeAl) project, which address trial design and analysis in small population clinical trials [34].

Furthermore, the establishment of large research networks using master protocols and the use of the pragmatic trial approach and Bayesian adaptive techniques could improve efficiency and safety in pediatric trials [35].

Well-designed and well-executed clinical trials have provided high levels of evidence. However, in a small population trial setting, the appropriate approach will need to be established on a case-by-case basis and will be mainly dependent on the perceived and potential advantages and disadvantages [20]. In this context, the use of novel clinical trial designs, such as a basket design, has recently been successful, allowing, for instance, the demonstration of the efficacy of tropomyosin receptor kinase (TRK) inhibitors in rare TRK fusion-positive cancers [36].

In addition, rigorous planning and early collaboration with regulatory authorities coud generate the best possible evidence base in an ethical and timely manner, which could lead towards

TABLE 2

Summary of research strategies for clinical research in rare diseases[a]

Aim	Specific aims	Strategy	Options	Description
Address small number of patients and outcomes	Minimize number of required participants	Study design	Factorial design	Two or more treatments can be simultaneously compared within a single group of study participants
			Response-adaptive randomization	Increases probability of participant's exposure to more effective treatment and decreases total sample size
			Sequential designs	Can identify differences in treatments before end of planned enrollment
			Crossover, N-of-1, alternating designs	Patients are their own controls, which guarantees treatment and improves statistical efficiency
	Make use of underpowered conventional studies	Statistical options	Increase α	Conventional thresholds might be insufficient in small sample sizes
		Incorporation into larger evidence context	Study conducted as part of prospectively planned meta-analysis	Individual small studies might not provide definitive evidence about a question, but can be combined to yield sufficient power
			Incorporate study into Bayesian framework	Small studies can help increase certainty around a clinical question
	Maximize outcome information among participants	Study design	Use continuous outcome	Increases statistical efficiency compared with binary outcomes
			Use surrogate outcome	Can be measured before patients are lost to follow-up for hard clinical endpoints
			Use composite outcome	Combining multiple outcomes into single endpoint increases number of events
			Use repeated measure outcome	Allowing patients to contribute with more than one event might increase total number of events
			Increase duration of follow-up	Longer studies allow capture of more outcome events among participants
		Recruitment and enrollment strategies	Focus on high-risk patients	Outcomes more likely to occur in high-risk patients
	Facilitate confounding adjustment with sparse data	Study design	Crossover, N-of-1, alternating designs	Patients are their own controls, which guarantees treatment and improves statistical efficiency
		Statistical options	Propensity scores	Can permit adjustment for more potential confounders than outcome regression modeling
Promote recruitment and retention	Maximize number of participants who receive treatment	Study design	Response-adaptive randomization	Increases probability of participant's exposure to more effective treatment and decreases total sample size
			Crossover, N-of-1, alternating designs	Patients are their own controls, which guarantees treatment and improves statistical efficiency
	Improve access to studies and participants	Recruitment and enrollment strategies	Trial networks and distributed data networks	Recruitment of larger and geographically diverse groups of patients in multicenter studies

[a] Adapted from Ref. [28].

optimization of the drug development program and higher acceptability of novel research methods. In this context, adaptive trial designs might allow more flexibility in the update of trial specificities, such as randomization scheme, number of treatment groups, and number and frequency of intermediate analysis [37].

Moreover, the knowledge and personal experiences from patients and respective caregivers might also be a useful tool for improved clinical trial design and outcomes. Such a strategy could provide valuable insights into the progress and management of the disease [13,22]. In fact, the lack of patient-reported outcome (PRO) tools has previously been suggested as an important challenge in neuromuscular clinical trials together with blinding issues, placebo use issues, and lack of guidance from regulatory authorities [38]. Recently, the European Organization for Rare Disorders (EURORDIS) called for the development and validation of PRO tools to support evidence of new treatment benefits, complementing the observer-reported outcomes (ObsRO) [39]. In this context, Gaasterland *et al.* [40] recently developed the POWER-tool, which aims to incorporate patients in the determination of outcome measures and of measurement instruments during trial design stage.

Towards addressing the small number of patients and outcomes in orphan drug trials, the Small Population Clinical Trials Task Force of the International Rare Diseases Research Consortium (IRDiRC) recently issued recommendations regarding trial design [13], where several strategies were proposed and grouped into six topics: (i) different study methods and/or designs related to specificities of medical conditions; (ii) adequate safety data and the importance of combining several sources of clinical data to provide a more complete picture of the safety profile; (iii) novel trial designs (e.g., multi-arm trials, platform trials, basket trials, and others); (iv) decision analytic approaches and rational approaches to adjusting levels of evidence; (v) extrapolation from pharmacokinetic/pharmacodynamic (PK/PD) modeling, registries, off-label data, and electronic patient records; and (vi) incorporation of patients' feedback into trial design, which is still a relatively new tool in orphan drug development.

Promoting patient recruitment and retention

Despite the inherent smaller nature of the population of an orphan drug trial, several strategies can be used to overcome this limitation, namely by: (i) maximizing the number of patients receiving the experimental drug (e.g., by using response-adaptive randomization); and (ii) improving accessibility to the studies and to participants' data by establishing trial and data networks [28].

Although the direct recruitment by the sponsor might be a more effective strategy than the typical researcher-driven recruitment, other strategies might help to improve patient recruitment, namely the distribution of printed and electronic information targeted at patients and their caregivers and a stronger collaboration with associations of patients with rare diseases [19].

The creation of databases of clinical registries of participants might also be a useful tool in rare diseases and safety monitoring, as recently shown by Stirnadel-Farrant *et al.* [41] for the case of Strimvelis, a novel *ex vivo* stem cell gene therapy for patients with adenosine deaminase-severe immunodeficiency (ADA-SCID). In addition, the use of registries in the rare disease research area might be useful [25] for improving the efficiency and quality of a clinical trial in earlier stages, such as trial design, by improving sample size calculation and expected disease course [42].

Concluding remarks

Clinical research involving therapies for rare diseases is challenging for several reasons, such as low disease prevalence, small and heterogeneous patient populations, difficulties in patient recruitment, and others. Diverse research strategies have been proposed to overcome such challenges and obstacles, namely improved study design, improved statistical analysis, incorporation into wide evidence context, and improved patient recruitment and enrollment. In addition, stronger collaboration with the regulatory authorities and the incorporation of the perspective of patients and caregivers might be key strategies to overcome clinical challenges in orphan drug development.

As a result of innovative methods and incentives for clinical research in rare diseases, the orphan drug market is expected to increase in the next few years and decades, thus improving its relevance in the global pharmaceutical market. Hence, further challenges might present themselves in the development of orphan drugs.

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