Designing clinical trials for rare diseases: unique challenges and opportunities

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Standfirst:

Orphan drug development is a rapidly expanding field. Nevertheless, clinical trials for rare diseases often present inherent challenges. Consequently, optimal study design and effective partnerships between academia and industry are central to the successful development, delivery, and clinical approval of effective therapies for this group of disorders.

Rare diseases collectively affect 300 million people worldwide[1] and over 6,000 distinct disorders are described. Most are genetic (72%), exclusively paediatric in onset (75%), and either life-threatening or severely disabling[1]. Studying rare diseases is challenging. Participant pools are small and restricted by rigid inclusion and exclusion criteria. There is often incomplete understanding of genotype–phenotype relationships and natural history to inform trial endpoint development. Finally, sensitive, non-invasive biomarkers and clinical outcome measures to monitor treatment responses are limited for many diseases.

Commercial interest in rare-disease medicinal products has flourished with scientific advances and legislation that incentivises drug development, such as orphan drug status. To date, 769 drugs for rare conditions have been approved by US and European agencies[2,3]. Orphan drug sales are predicted to rise from $119 to $217 billion by 2024[4], with a surge in clinical trials anticipated. To obtain orphan drug approval, substantial evidence of clinical safety and efficacy is required. Trial design requires an appropriately powered sample size, control group, validated biomarkers, and clinically meaningful outcome measures. For rare diseases, strategies exist to overcome the methodological challenges posed by these constraints.

[H1] Trial power

The power of a trial is maximised by increasing the number of subjects. This is not always feasible in rare diseases due to practical and ethical limitations, especially in paediatric populations. In orphan drug trials, the size estimate of a likely effect should be calculated at a reasonable power of 80% and 5% confidence interval. In ultrarare conditions, an 80% power may not be *a priori* achievable, necessitating work with regulatory agencies to develop acceptable alternative trial parameters. Creative approaches that allow reduced participants and study duration have been developed because conventional, parallel, randomised controlled trials are not always feasible (Table 1). The certainty of exposure to active treatment reduces ethical issues and favours patient participation in the trial.

Sample size reduction and optimised recruitment are achieved by: extending trial duration to increase events captured per patient; reducing disease heterogeneity through identifying subjects likely to experience poor outcomes and selecting participants who are likely to

respond to treatment; and maximising study access using broad networks, which facilitate the conduct of multicentre and/or multinational trials and expedite patient recruitment. For example, the North American Mitochondrial Disease Consortium (NAMDC) has recruited over 1,600 patients in eight years[5], and the United Kingdom Mitochondrial Disease Patient Cohort (MitoCohort, REC: 13/NE/0326) almost 2,000 patients over 12 years. Both have collected natural history data and contributed to the development of new diagnostic techniques, clinical guidelines, and new therapy trials for primary mitochondrial diseases (PMDs).

To accelerate drug approval for serious rare diseases without alternative treatments, Phases 1–3 of clinical trials can be adapted to integrate traditional Phases 2 and 3 within a single study design. This was successfully adopted to test the efficacy of elamipretide in Barth syndrome[6], a PMD characterised by impaired cardiolipin metabolism, with approximately 200 living affected males worldwide. Compassionate usage accelerates orphan drug application, particularly for seriously debilitating and/or life-threatening conditions. In this scenario, an unauthorised medicine (often involved in Phase 3 trials near completion or pending market authorisation) is made available to patients who are ineligible for clinical trials and have diseases with no licensed therapies. One example involved imiglucerase, donated to hundreds of patients with Gaucher disease.

[H1] Control groups

External controls can be used when the disease is severe with no alternative treatment, or when a placebo is inappropriate. Concurrent are preferred to non-concurrent external controls, as bias is minimised. Natural history data can be used as the control of a treated group[7], but only if the two groups have similar disease characteristics, including severity, illness duration, and prior treatments. Historical cohorts and registries may not include endpoint data unless designed prospectively.

The application of natural history data for drug development is not limited to the identification and stratification of appropriate patients to participate in the trial, or provision of an external control population, but may also be pivotal in the development and validation of biomarkers and clinical outcomes measures.

[H1] Biomarkers and outcome measures

Biomarkers serve as surrogate endpoints in clinical trials and help predict the clinical benefit or harm of an intervention. They require validation, which depends upon demonstration of responsiveness to an interventional treatment or disease progression, a process supported by the FDA's Drug Development Tools biomarker qualification program[8]. Fluctuations in biomarkers may precede clinical parameters — particularly in slowly progressive diseases — thus, their inclusion in trial design can shorten time to market authorisation for new drugs. Several biomarkers have been applied in pivotal studies that ultimately led to drug approval; for instance, the reduction of globotriaosylceramide deposits in the kidneys of patients with Fabry disease treated with migalastat[9]. Despite their advantages, biomarkers often reflect a single pathophysiological pathway and provide limited data concerning the drug effects on other aspects of efficacy. Additionally, there is potential for off-target, negative effects of the intervention to be overlooked.

Continuous outcome variables are increasingly used over binary or hard clinical endpoints, given their greater sensitivity to change over time; the percentage change of a continuous measurement is preferred over the dichotomisation of patients as responders or non-responders. When hard clinical endpoints are preferred, they should be combined into a single composite measurement (such as a multidimensional responder index[10]) to increase the number of observed events. The analysis of repeated measures derived from longitudinal data is recommended, whenever possible, as it leads to a reduction in sample size by diminishing the variance of estimated treatment-effects.

In conclusion, innovative solutions are helping address the inherent challenges of conducting interventional studies in rare diseases. Partnerships between academia and industry facilitate optimal trial design through appropriate stratification of patients, optimising participation, and treatment effect measurements. Although stringent inclusion criteria may maximise the likelihood of meeting primary endpoints, the data may not be applicable more broadly or to a real-world population. Trial-related patient fatigue must be considered and priority afforded to interventions with the maximum probability of conferring clinically meaningful benefits.

Competing interests

The authors declare no competing interests.

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Table 1. Main clinical trial design options for rare diseases.

Trial design	Main characteristics	Advantages	Disadvantages
Parallel group randomisation	Participants randomly allocated to one of two or more treatment groups	Gold-standard; Minimises selection bias and confounders	Large sample size; Long follow-up; Not always feasible in rare diseases
Cross-over	Participants randomly receive a sequence of different treatments, each followed by a wash-out period; Participants act as their own control	Maximises number of on-treatment participants; Participants receive all interventions	Only applicable for stable diseases with short treatment duration; Carry-over effect
Delayed start	Initial randomised placebo-controlled phase, followed by a second phase during which all participants receive active treatment	All participants receive active treatment; Can be used to assess disease progression and relapses	Double-blinding in first phase only; Carry-over effect from first to second phase
Randomised withdrawal	All participants receive open label treatment during first phase to identify responders; Only responders are randomised to treatment or placebo during second phase	Time of exposure to ineffective treatment and placebo is reduced	Overestimation of treatment effect (only responders included)
Group sequential	The number of participants is not set in advance;	Reduced sample size;	Limited efficacy data in subgroups when

	Clinical trial data are monitored through pre-determined interim analysis; Trial can be terminated early according to interim analysis	Potential for identifying early efficacy; Flexible methodology	trial terminated early
Adaptive	Probability of randomisation to one group shifts towards more promising treatments, according to results obtained from previous participants	Reduced sample size; Flexible methodology; Increased probability of receiving most effective treatment	Time required for study design; Appropriate analysis required to estimate treatment effect and control type I error