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The challenges of clinical trials in rare diseases

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Undertaking any clinical trial can be laden with obstacles and challenges. Both commercial trials and academically sponsored studies share questions around trial design, recruitment targets, mitigating dropout and, ultimately, challenges of regulatory approval if the bar for efficacy and safety are met. However, trial design and delivery in the rare disease arena bring specific considerations and potential pitfalls, for researchers, patients, pharma and regulators. Anticipating these ahead of trial design and setup can increase the chances of success and the ultimate goal of an investigational product reaching market.

In the USA, a rare disease is defined as one that affects no more than 200 000 individuals nationwide (a prevalence of roughly six per 10 000)[1] and in Europe has a prevalence of up to five per 10 000, or around 250 000 individuals affected.[2] Although individually rare, there are around 7000 distinct rare diseases, 80% of which are genetic, meaning around 30 million in the USA, and a similar number in the European Union (EU), have a rare disease, of whom around half are children. Current treatments are usually supportive rather than disease-modifying, leaving most patients with rare diseases with considerable unmet medical needs.[3,4]

By necessity, many rare disease clinical trials are multicentre, often multinational, for sufficient patient recruitment, even in phase I and II trials. This can challenge protocol harmonization, ethical review, indemnity, organization of clinical services, standards of care and cultural diversity.[5] Language differences and working across varied time zones can add complications. For academic-sponsored studies, without assistance from a commercial research officer, the administrative load of undertaking multicentre rare disease trials can be a powerful disincentive. Potential participants may also be discouraged; disease reference centres may be few and far between, meaning significant time and cost for individuals to attend trial visits. Additionally, requirements of the trial itself, such as taking additional medication, completing diaries, recording symptoms or side-effects, adds to the daily disease burden that patients already face.

Selection of meaningful and relevant endpoints is fundamental to rare disease clinical trial design and requires an understanding of the natural history of the disease, of the normal trajectory without intervention or with standard of care for comparison. However, rare diseases are heterogeneous and a detailed knowledge of their natural history is often lacking, compounded by variable expression within diseases and subtypes, often reflecting factors such as a specific genotype. In addition, they are often complex, involving many systems, further challenging endpoint selection. Regulators may ask for outcome measures from trials of more prevalent disorders but differences in disease mechanisms can invalidate these decisions. For example, a primary endpoint of time to wound closure widely adopted in studies of diabetic, pressure or venous ulcers has been used in some recent clinical trials of epidermolysis bullosa (EB).[6,7] However, this ignores the nature of EB wounds whereby they heal, but then break down again as a result of the underlying molecular defect affecting dermal–epidermal cohesion.[8]

Outcome measure selection should reflect relevance and significance for the patient; this may be diminished pain or itching, or a reduced requirement for daily care, and may include a relevant patient-related outcome measure. However, for many rare diseases, the magnitude of change in a parameter that makes it meaningful for a patient has not been explored. Without this, knowing what constitutes a 'therapeutic success' could be based ostensibly on guesswork. Endpoints should also support sufficient powering where numbers of participants will be limited by disease rarity. Selection of measures or events expected to show only small changes or occur infrequently run the risk of failure to demonstrate effect over the course of a trial.

While a double-blind placebo-controlled randomized trial remains the gold standard, limited potential participants and phenotypic heterogeneity in rare diseases may confound this.[9] Where existing treatment options for a rare disease are limited or nonexistent, patients would usually prefer access to an active intervention rather than the possibility of just placebo. Crossover studies and those with an open-label extension can address this. In diseases where disease morbidity and mortality are high, it may be unethical to use a placebo or difficult to ascertain necessary blinding. Various enrichment approaches can select trial participants most likely to demonstrate any effect (or lack thereof) of a treatment, for example by prospectively identifying patients likely to complete a trial or excluding those with unstable disease.[10] Adaptive trial design, where the protocol is amended and refined as the trial progresses according to responses, is another possible approach where trial participants are limited. External controls can also be used in randomized controlled trials (RCTs), either from observation prior to enrolment or from cohorts from published or registry data. Statistical techniques using counterfactual analysis can be used to augment observational data in an RCT, exploring what would have happened without an intervention. Alternatively, single-patient studies in rare diseases may generate data that can later be subject to metanalysis.

With children comprising half the rare disease population, trials in this age group may entail additional ethical or regulatory considerations. Where adults have a disease, regulators may require early trials to be conducted in these first, before expanding to adolescents and children. However, some rare

diseases may have significant mortality in childhood or have irreversible complications if not addressed in early years, necessitating clinical trials in children from the outset.

The Orphan Drug Act of 1983 was passed by US Congress to give financial incentives to pharmaceutical companies including market exclusivity and tax breaks to develop drugs for rare diseases,[1] with similar legislation passed in the EU[11] and elsewhere. The US Food and Drug Administration has also supported a fast-track programme for more rapid acceleration to phase III trials and rare disease drug approval. Over the last 30–40 years, the number of designated orphan drugs for rare diseases has increased more than fourfold, with an upward trajectory, indicative of the expansion of novel drugs and biologics for a multiplicity of rare conditions.[12]

Despite the potential hurdles of rare disease clinical trials, international collaboration through organizations such as the International Rare Disease Research Consortium (IRDiRC), comprising patient advocacy groups, nongovernmental agencies, funding bodies, researchers and companies, is driving progress towards improved diagnosis and treatments for people living with rare diseases.[13] Regulatory bodies are starting to acknowledge that endpoint selection may not be straightforward and that understanding the natural history of the rare disease is critical. The patient voice is also key in determining meaningful outcomes and, in this respect, patient groups and alliances such as the Genetic Alliance UK or the National Organization for Rare Disorders (NORD) in the US are invaluable. Comprehensive patient registries with phenotypic and, where relevant, genotypic data, are also key to identifying potential trial participants. When considering a rare disease study, early involvement with clinical trial design experts familiar with the challenges of this work with biostatistician input is vital. Finally, using opportunities to discuss trials with regulators in advance will help inform study design to better align to the questions that will need to be asked in order to gain approval.

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