CRITICAL PATH INSTITUTE

Overcoming the challenges of rare disease clinical research

Abstract

Development of drugs to treat rare diseases faces unique challenges. Traditional placebo-controlled clinical trials may be difficult to enroll because of small source populations or concerns with using placebo arms. Non-traditional trial methods may be complicated to implement because of lack of regulatory precedent or investigator experience, along with limited understanding of the natural history of the disease required to inform statistical analysis plans. Regulatory-endorsed clinical outcomes assessments and biomarkers may not be readily available in some rare diseases. For these reasons, the benefits and risks of treatments for rare diseases are more difficult to estimate. Despite these challenges, treatments for rare diseases have been developed and granted regulatory approval, but there remains considerable need to further innovate clinical trial designs, regulatory approval processes, and reimbursement evaluations. Collaboration among industry, clinicians, researchers, regulators, payers, and patients provides the best framework for developing evidence applicable to a rare disease and demonstrating clinically meaningful benefits of an investigational drug. Critical evaluation of evidence requirements in rare diseases is warranted to identify novel ways to drive innovation and efficiency in bringing new therapies to market. This review focuses primarily on clinical development and regulatory evidence-generation strategies for rare diseases, while also highlighting how residual uncertainty may affect subsequent health technology assessment, reimbursement, and access decisions. We provide examples of drug approval processes and outline various potential strategies for clinical development of rare disease treatments, highlighting the strengths of each technique and discussing the opportunities to enhance clinical research.

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