White Paper

Natural History Studies for Rare Diseases: Development Strategies for External Comparator Arms Leveraging Real World Insights

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Executive summary

Natural history studies have historically been used by clinical researchers to understand disease progression in poorly characterized diseases. More recently, these studies have been re-purposed in a variety of ways to facilitate clinical development in rare disease. These include serving as external comparators to support rare disease treatment approvals when it is unethical or unfeasible to evaluate the treatment with a randomized controlled design.

When these real-world, protocol-driven studies are integrated into the early clinical development planning process, they can accelerate drug development, improve the odds of regulatory approval and reimbursement, and bring new life-changing treatments to patients in need.

This paper explores essential principles for defining the right strategy for natural history studies and how to design such studies in a way that the data can be used as an external comparator to augment future regulatory filings and payer submissions.

Introduction

The rare disease pharmaceuticals landscape is undergoing revolutionary change. The industry is making unprecedented investments in the development of innovative therapies and embracing novel trial designs in an effort to reduce time-to-market, in turn bringing much needed treatments to patients with rare disease who often have no existing treatment options. These investments are paying off. In 2019, just over half of new active substances received an orphan drug designation at time of approval.[1]

Many of these new therapies benefit from fast track approval programs for breakthrough therapies, designed by regulators to speed new drugs to market.[2] To achieve this accelerated approach, developers must first deepen their understanding of disease progression, population heterogeneity, the patient and caregiver perspective, and the current standard of care when one exists. These insights can be gained through natural history studies.

In a March 2019 guidance document on natural history studies in rare disease drug development, the FDA defines natural history studies as "observational studies that collect information about the natural history of a disease in the absence of an intervention, from the disease's onset until disease resolution or the individual's death."[3] These studies can be more valuable than relying on data gathered from disease registries because they allow researchers to answer specific questions beyond standard of care data collection. These include identifying potential biomarkers and querying patient-reported outcomes (PROs) and quality-of-life measures to identify the most relevant endpoints for future studies. When developers incorporate natural history studies into their rare disease drug development plan, the insights can be used to optimize clinical planning, support regulatory alignment, and provide the longitudinal data needed to support single arm trials.

Natural history studies support multiple clinical development objectives in rare diseases.

1. Evaluation of the current standard of care or treatment options
2. Estimation of disease prevalence
3. Identification of biomarkers to diagnose the disease
4. Identification of predictors of disease progression
5. Evaluation of potential clinical endpoints
6. Development of Clinical Outcome Assessments (COAs) and relevant PROs
7. Identification of the target patient population, including possible patient subgroups, for future clinical studies
8. Establishing a baseline for future use as an external or historical comparator in clinical studies

HOW NATURAL HISTORY STUDIES SUPPORT RARE DISEASE RESEARCH

Rare disease drug development faces several significant obstacles that natural history studies can help to address. These include:

1. **Limited knowledge about underlying disease mechanisms and clinical progression.** In rare diseases, the natural history of the disease, including variability in clinical features, is not always well understood. Natural history studies can provide important insights, including helping to define genotype/phenotype relationships, identifying appropriate subpopulations for a trial, and identifying PROs, such as which symptom relief is most important to patients and caregivers. These insights help to drive more successful drug development.

2. **Undefined clinical endpoints:** Many rare disease trials are hampered by the absence of well-validated biomarkers, endpoints, and outcome measures. This is particularly common when companies enter a disease area in which no drug development has occurred. Natural history studies can be used to develop or validate biomarkers and to establish the most relevant trial endpoints, including surrogate endpoints.

3. **Patient and site engagement:** An obvious challenge for many rare diseases is small, globally-dispersed patient pools. Identifying rare disease patients and research sites often necessitates a broad approach beyond diagnosis codes, including mining insights from the academic landscape, centers of excellence, and patient advocacy groups. A well-planned natural history study helps to identify patients for future interventional trials, expediting subsequent recruitment by pre-identifying individuals interested in receiving the investigational product. Simultaneously, companies can build relationships with trial sites and key opinion leaders and leverage their thought leadership during the therapy development process.

4. **Post-marketing commitments:** Smaller sample sizes and accelerated approval pathways often require post-marketing studies and benefit-risk management. Natural history studies or registries are often used for this purpose at the end of the development lifecycle of a rare disease product.

VALUE OF EXTERNAL COMPARATOR DATA IN RARE DISEASE DEVELOPMENT

An external comparator (EC) is a patient cohort derived from data external to a research study or "index trial". ECs are also commonly referred to as "external controls", "historical controls", or "synthetic controls."[4]

In rare disease therapy development, where there are typically no available alternative treatments, a randomized controlled trial design with a portion of participating patients randomized to an internal control (e.g. placebo) is often not appropriate. This occurs because it may be unethical to randomize patients to receive placebo, patients may be unwilling to participate due to the risk of not receiving the investigational therapy, and/or low patient numbers due to the rarity of the indication may preclude a control group.

For development programs that have invested early in the conduct of a natural history study, that study data can be re-appropriated as an EC arm for a single-arm clinical trial. This clinical development strategy ensures all eligible patients can receive the investigational therapy, which encourages patients to participate in research while being ethically sound.

External comparators are not a methodological equivalent to a randomized controlled design, but when designed correctly can provide a valid comparator to generate regulatory-grade evidence. However, when randomized clinical trials are unethical or infeasible, ECs can provide comparative context by demonstrating how a similar patient group performs when not receiving the investigational therapy. ECs, which can be constructed from natural history study data, provide comparative evidence by simulating a control or comparator arm in a research study. The EC is constructed by identifying patients from real-world data (RWD) who are similar to the research study population based on the study eligibility criteria, with equal ascertainment (as possible) of exposures, outcomes, and confounders.

While ECs can add value across the development program, a core focus today is their use as control arms alongside single-arm trials to support regulatory filing and reimbursement submissions. This use case is becoming increasingly common in rare disease therapy development.

External comparators have been used in rare disease drug development sporadically for some time, typically in the form of historical benchmarks from literature. However, evolving standards for real-world research

give us the opportunity to proactively acquire data on patients more precisely aligned to the future trial patient population, which increases the robustness of the comparative analysis. A forward-thinking natural history study can serve as a robust data source from which to derive an EC population.

CURRENT PRECEDENT AND OPPORTUNITY TO SPEED DRUG DEVELOPMENT

The regulatory and health technology assessment (HTA) landscape is becoming more accepting of RWD to support decision-making. This is increasing the use of trials that incorporate external comparators from RWD. For rare disease drug development, draft guidance for industry released by FDA in January 2019 describes that in situations where it is unethical or impractical to randomize to an internal control arm, well-designed natural history studies can serve as an external control group for a single-arm trial. FDA qualifies the appropriate application of an external (or historical) control as "when (1) there is an unmet medical need, (2) there is a well-documented, highly predictable disease course that can be objectively measured and verified, such as high and temporally predictable mortality; and (3) there is an expected drug effect that is large, self-evident, and temporally associated with the intervention."[5] This approach is in agreement with considerations for use of external comparator as outlined in ICH E10 guidance,[4] which is internationally recognized and adopted.

While many of the more recent adopters of external comparators from natural history studies have not yet reached regulatory filing and are therefore are not available as case studies, there is an increasing body of evidence indicating this type of approach is viewed more favorably by regulators. Two case examples are discussed below.

Case study 1

In 2017, BioMarin's Brineura (cerliponase alfa), which treats late infantile neuronal ceroid lipofuscinosis type 2 (CLN2), received regulatory approval based on a non-randomized trial that compared 22 symptomatic patients to an external control of 42 untreated patients from a natural history of disease study. Brineura received favorable opinion on April 21, 2017 from the Committee for Medicinal Products for Human Use (CHMP) of the European Medicines Agency (EMA) and was approved on April 27, 2017 by the US FDA.[6]

Case study 2

Zolgensma (onasemnogene abeparvovec) was approved by the FDA on May 24, 2019 for the treatment of pediatric patients up to the age of 2 with spinal muscular atrophy (SMA). Efficacy was evaluated in an open-label, single-arm clinical trial and an open-label, single-arm, ascending-dose clinical trial with comparisons made to a natural history of disease cohort of 34 SMA patients. The FDA label for Zolgensma describes the importance of the external comparator in stating, "comparison of the results of the ongoing clinical trial to available natural history data of patients with infantile-onset SMA provides primary evidence of the effectiveness of Zolgensma."[7] It received subsequent approval from Japan's Ministry of Health, Labor and Welfare in March of 2020 and it remains under EMA review."[8]

WHAT ABOUT REIMBURSEMENT?

Using IQVIA's Health Technology Assessment Accelerator database, which catalogues HTA appraisals from 100 HTA Agencies in 40 different countries, IQVIA analyzed trends in the use of single-arm pivotal trial designs and the impact of external controls on reimbursement decision-making. Between 2011 and 2019, IQVIA has observed a 13x increase in submissions to HTAs that rely on single-arm pivotal trial data. Of these submissions, 52% contained external control data.

After assessing the outcomes of these submissions, IQVIA found a significantly higher likelihood of positive reimbursement outcomes when an HTA submission with single-arm pivotal data also incorporates an external control from real-world data. Prospectively designed natural history studies can provide particularly robust external control data to support successful reimbursement, ultimately reducing time to market and becoming broadly accessible to patients who need these valuable therapies.

As a result of growing regulatory acceptance of external comparators, there is increasing precedent in their acceptance for HTAs in support of reimbursement decision making. We expect to see continued expansion in the use of natural history study data to supplement pivotal trial submissions for rare disease treatments.[9] Furthermore, programs incorporating single-arm trials with ECs are likely to recruit and read-out more quickly than randomized controlled studies as these designs require fewer patients, and remove a key barrier to trial participation: risk of randomization to placebo.[10] With growing evidence of the acceptability of natural history studies by regulatory agencies, these programs could see a faster pathway from discovery to drug approval, ultimately putting essential medicines in the hands of patients who may have not have alternative options. While this approach offers great promise to companies, anticipated use of natural history studies as a future external comparator must inform the way each study is designed to maximize the robustness of future comparative analyses.

Design considerations

Anticipating that a natural history study will be used to provide additional comparative context for a pivotal single arm trial may streamline the development process and minimize site and patient burden. However, it is important that the natural history study be timed to provide relevance as a comparator for clinical research. If a natural history study precedes initiation of first-in-human trials, the study may be completed years before it will be used in a regulatory submission. That may cause the relevance of the historical data to become questionable if there are significant changes in standards of care or critical outcome measures during this time.

There are several design considerations and operational strategies for NHS planning.

WHAT DATA WILL NEED TO BE COLLECTED TO DEFINE THE COMPARATOR COHORT?

This includes variables to help identify patients based on key eligibility criteria, potential endpoints or confounders of interest, subgroups that are likely to have better outcomes, and indicators of disease progression. Early clinician judgment and collaboration with key opinion leaders are essential to anticipate critical data variables that will likely be needed in a future clinical trial program. This ensures that researchers will collect those variables as part of the natural history study.

WHERE WILL STUDY DATA COME FROM?

A prospective natural history study can offer enhanced data collection beyond standard of care (e.g., biomarkers), and potentially include data reported directly by patients and/or caregivers. While it can be tempting to ask patients for every possible detail to gain detailed knowledge about disease progression, it is important to weigh the value of each datapoint against the burden of collection. Asking too many questions, or requiring too much time, can negatively impact data quality and study retention.

If the natural history study uses retrospective data collection (i.e., medical chart abstraction), researchers will be limited to the standard of care, and secondary data sources may vary in quality and completeness of relevant information. However, if the data proves to be sufficient, this data can be extracted and analyzed more quickly.

While analysis of existing data may be appropriate in certain situations, we recommend a prospectively designed natural history study where feasible, as it is viewed to be more robust by regulatory authorities according to FDA Guidance.[3]

WHO NEEDS TO BE INVOLVED IN PLANNING?

Natural history studies that are intended to be used as an external comparator should include the appropriate cross-functional reviews by specialty clinicians, epidemiologists, biostatisticians, and patient representatives. Where possible, patient advocates should be included in early design and data collection decisions to identify potential hurdles to the current plan and to reinforce the message that they are partners in the clinical development process. Potential trial endpoints and patient eligibility criteria should be reviewed by these experts to ensure adequate sample size and data quality needs for future external comparison.

Design of natural history studies should involve epidemiologists and biostatisticians who are trained in the comparative analysis methods of clinical and RWD. These experts can provide essential insights into how to create a methodologically sound approach that will compare with a trial population.

Avoid interventional trial pitfalls and achieve early regulatory alignment with data from a properly timed natural history study

Characterize rare disease or rare subtypes

Develop surrogate endpoints

Plan interventional trial

Form patient pool for interventional trial recruitment

Establish trial endpoints

Build relationships with sites and KOLs

Conclusion

A well planned and executed natural history study can lead to greater understanding of the underlying disease and function as a valuable comparator arm for rare disease studies. However, designing an effective natural history study requires early planning, robust collaboration between all relevant stakeholders, and a custom approach to ensure the patients included and the data collected will be appropriate to serve as a future comparator for the clinical trial program.

Ultimately, accelerated approvals of much-needed therapies benefit the patients waiting for alleviation or cure of their conditions. Given the increased openness to using real world data to inform regulatory and HTA decision-making, IQVIA anticipates expanded use of natural history studies as future ECs, and we are designing our natural history studies with this potential future use case in mind. These proactive planning and design steps help to maximize the return on research efforts and ensure patients get access to much needed treatments as quickly as possible.

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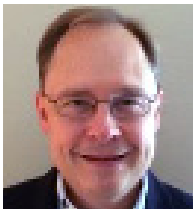

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