



More Insight from Fewer Patients: Advancing Rare Disease Trials with the Net Treatment Benefit

Rare disease clinical trials face a confluence of challenges: limited patient populations, heterogeneity in disease progression, and often a lack of established outcome measures. Yet the stakes involved are exceptionally high. For the over 300 million people living with a rare disease worldwide,¹ most of whom lack access to effective therapies, each trial represents a vital opportunity – not just to generate evidence, but to shape treatments that meaningfully improve the patients' lives.

Traditional clinical trial designs, typically focusing on a single primary endpoint, are often ill-suited for this complex task. They frequently simplify the multidimensional reality of how patients, caregivers, and clinicians define meaningful treatment benefit into a single dimension. For instance, a therapy may slow disease progression but negatively impact quality of life; it may show modest improvement in the main endpoint yet substantially improve fine motor functions or reduce intolerable side effects. In rare diseases, where patient numbers are limited and the burden of participation is high, trials must do more than test hypotheses – they must produce data that reflects what matters most to those affected.

The Net Treatment Benefit (NTB) emerges as a patient-centric, statistically rigorous approach that allows for the prioritisation and integration of multiple outcomes into a single, interpretable measure of treatment effects.² When coupled with early engagement from patients, investigators, and key experts to define outcome hierarchies, NTB offers a practical path to trials that are both more efficient and more aligned with real-world needs.

The Challenge of Endpoint Selection in Rare Diseases

One of the most persistent bottlenecks in rare disease trial design is the selection of an appropriate primary endpoint. In common conditions, regulatory precedent and existing clinical guidelines typically point the way. In rare diseases, the path is often uncharted.

Consider Pompe disease or Duchenne muscular dystrophy. Patients, families, and clinicians may prioritise very different outcomes depending on the disease stage: respiratory function, ambulatory capacity, ability to feed independently, fatigue, or even cognitive symptoms in syndromic variants. Designing a trial around one of these clinical outcomes risks overlooking the others – and worse, dismissing a therapy that offers multidimensional benefit simply because it falls short on a single axis.

This issue becomes more acute when regulators require “hard” clinical outcomes, such as time to death or forced vital capacity, that may not be the most relevant for early- or mid-stage patients. Many rare diseases progress slowly or unpredictably, making it difficult to observe changes in a single outcome within the limited duration of a trial.

By forcing sponsors to choose one outcome as the sole measure of success, traditional designs risk misrepresenting the true value of an intervention. This not only complicates regulatory evaluation but can discourage further investment in promising therapies.

Why Net Treatment Benefit Is a Game-changer

Net Treatment Benefit, grounded in the methodology of Generalised Pairwise Comparisons (GPC), offers a solution to these challenges. Rather than selecting a single endpoint, NTB enables trials to incorporate multiple outcomes – each assigned a position in a pre-defined hierarchy reflecting clinical and patient priorities.

In essence, NTB calculates the difference between the probability that a randomly selected patient in the treatment group does better across the prioritised outcomes than a randomly selected patient in the control group, and the reverse. This yields a single, interpretable statistic that reflects the totality of the evidence.

The statistical advantages are compelling. By incorporating multiple relevant outcomes into the analysis simultaneously, NTB makes fuller use of the collected patient data, effectively capturing more comprehensive information about treatment effects. This is especially critical in rare disease trials, where small sample sizes are the norm. More efficient use of available data means improved power to detect clinically meaningful differences – potentially with fewer patients or shorter trial durations.

Specifically in the rare disease domain, a post-hoc analysis of the randomised, double-blind, phase 3 COMET trial, prioritising the primary (forced vital capacity) and secondary outcome (6MWT), provided evidence of efficacy of avalglucosidase alfa therapy ($n = 51$) over alglucosidase alfa ($n = 49$) in Pompe disease, while the original analysis failed to significantly show superiority of treatment on the primary endpoint.³

Prioritising Outcomes with Stakeholder Input

What truly sets NTB apart is not just its statistical sophistication, but its ability to formalise clinical and patient preferences in the design phase of a trial.

In rare diseases, the need for such an approach is acute. Disease burden varies widely across individuals, and the diversity of symptom trajectories makes a one-size-fits-all endpoint inadequate. Engaging stakeholders early – patients, caregivers, site investigators, and treating clinicians – enables trial sponsors to co-create outcome hierarchies that reflect the lived experience of the disease.

Structured preference elicitation methods, such as discrete choice experiments or ranking exercises, can yield clear insights into which outcomes matter most and in what order. However, these traditional approaches can be cumbersome, often requiring large numbers of respondents. Innovative methods are therefore needed to simplify

the process and reduce the burden, especially in rare diseases with limited patient populations.

By building consensus around outcome prioritisation upfront, sponsors not only create trials that are more meaningful – they reduce the risk of post-hoc disputes about relevance and increase the likelihood that trial data will resonate with regulators, payers, and clinicians.

Reducing the Burden on Patients and Families

Rare disease trial participants and their families often carry a disproportionate burden: frequent travel, complex assessments, and uncertainty around the value of their contribution. Any opportunity to streamline trials without compromising scientific integrity is not just a design consideration – it's imperative.

NTB can reduce this burden in two important ways. First, by increasing statistical efficiency, NTB-based designs may require fewer patients to reliably detect whether a treatment is truly effective. Second, by allowing multiple outcomes to contribute to the primary analysis, NTB helps ensure that more of the collected data is meaningfully used, reducing waste and enhancing the value of each patient assessment.

Moreover, NTB allows the inclusion of clinically meaningful thresholds – minimum differences that matter to patients – in the analysis. This means that only differences considered meaningful are used to distinguish between outcomes, while smaller, less relevant differences are treated as neutral. This helps the analysis focus on what truly matters and adds another layer of patient-centricity, ensuring that the trial's conclusions reflect not just differences, but meaningful ones.

Supporting Regulatory and HTA Pathways

While the NTB has yet to become a standard primary analysis method in rare disease regulatory submissions, it is already well established and familiar to regulators in other therapeutic areas.

The ATTR-ACT trial for transthyretin amyloid cardiomyopathy used an NTB-like approach to prioritise time to death over time to hospitalisation – highlighting how multidimensional benefit-risk profiles can be formalised in regulatory-grade evidence.⁴ As regulatory agencies continue to emphasise patient-focused drug development (PFDD),⁵ particularly for conditions where unmet need is high, there is a growing appetite for approaches that reflect the real-world complexity of treatment benefit.

Importantly, NTB is also well-suited for health technology assessments (HTAs). These bodies are increasingly requiring quantitative evidence of value beyond clinical efficacy – especially in Europe and Canada, where quality-adjusted life years (QALYs) and other composite measures are common. Because NTB summarises multiple prioritised outcomes into a single interpretable measure, it aligns well with the demands of HTA dossiers and payer value frameworks.

In rare diseases, where treatments are often high-cost and subject to scrutiny, demonstrating comprehensive benefit-risks balance quantitatively is critical not only for approval but for access.

Fostering Adoption and Continuation of Development

An often-overlooked benefit of NTB in rare diseases is its potential to de-risk development decisions. When phase 2 trials are underpowered due to small sample sizes, NTB can detect more signal from limited data. Sponsors can make better-informed go/no-go decisions, reducing the likelihood of prematurely abandoning promising therapies or investing heavily in interventions with narrow appeal.

In turn, this supports better engagement with investors and partners. A clear, well-structured NTB analysis – grounded in patient and clinician priorities – can be a persuasive element in fundraising and partnership discussions. It also supports clinicians in understanding which patients are most likely to benefit, based on outcomes that mirror their own treatment goals.

Conclusion: Making Rare Disease Trials Work for Patients

For decades, rare disease trials have struggled under the weight of conventional clinical trial methodologies not designed for their constraints. The use of a single endpoint often obscures meaningful multidimensional benefits. It increases the likelihood of inconclusive results, slows development, and most importantly, can fail to serve the patients who volunteer their time, energy, and hopes.

Net Treatment Benefit, supported by robust stakeholder engagement in the selection and prioritisation of outcomes, offers a viable, scalable, and scientifically rigorous solution. It allows for the integration of what matters most – survival, function, quality of life, and tolerability – into a single evaluative framework. And in doing so, it makes trials more efficient, more informative, and more aligned with real-world treatment decisions.

As the rare disease community continues to push for faster, more meaningful innovation, the integration of NTB into early trial design is not just a statistical refinement. It is a strategic imperative – one that places patients, not endpoints, at the centre of progress.

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Tom Mann is a Clinical Solutions Engagement Lead at One2Treat. He brings over 15 years of experience in tech start-ups and scale-ups, where he played a pivotal role in driving customer engagement, marketing initiatives, and strategic partnerships. At One2Treat, Tom's expertise and fresh perspective are invaluable as we continue to develop solutions that integrate key patient-relevant outcomes into a single holistic treatment assessment. With a strong background in SaaS companies, Tom has a deep understanding of customer needs. His ability to translate those needs into actionable solutions will be essential in expanding One2Treat's reach and impact within the clinical research landscape. At the same time, he ensures that our approach remains both innovative and patient-focused.

