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EDITORIAL

Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Trials

The International Society for Pharmacoeconomics and Outcomes Research Task Force has presented a detailed report highlighting the challenges associated with capturing clinical outcomes assessments (COAs) in rare disease clinical trials [1]. The exponential rise in the development of orphan drugs, together with the likelihood of fast track regulatory submissions and the increasingly refined standards associated with COAs for use in clinical trials, culminates in a raft of challenges related to the capture of relevant, meaningful, and valid COA-related treatment benefits in these populations. As such, the work of this task force is paramount to help highlight challenges associated with data collection required to support regulatory submissions and to begin to explore creative solutions to these challenges.

The stated objective of this particular task force report is to describe emerging good practice recommendations for addressing the challenges inherent in identifying, selecting, developing, adapting, and implementing COAs for use in rare disease clinical trials [1]. The scope of the report is, however, refined to exclude issues related to trial design, or COA data-related economic or value assessments.

Given the focus of the report on the use of COAs in a clinical trial setting as efficacy end points, the article is structured in line with the US Food and Drug Administration's (FDA's) Roadmap to Patient-Focused Outcome Measurement in Clinical Trials [2]. With the highlighted challenges and proposed solutions addressed under each of the three key roadmap headers—1) understanding the disease or condition; 2) conceptualizing treatment benefit; and 3) selecting/developing the outcome measure—the roadmap adopts the terminology of the FDA's qualification guidance [3] to provide more complete context-driven or applied guidance to the development, selection, and use of patient-reported outcomes described in the original FDA guidance [4].

There is a potential problem in adopting this approach, because all challenges and solutions identified are embedded in the standard FDA approach to COA development, and use some very well-trodden and established methodological approaches. Well-trodden and established is by no means bad, current standards are high and translate into sound scientific rigor. But arguably, rare diseases may require thinking beyond such constraints. One example is the issue of sample size, which is especially important considering that approximately 75% of rare diseases affect children, and 30% of these children do not live beyond the age of 5 years [5].

The challenges identified in the report include such issues as heterogeneity in disease presentation and patient experience, poor/incomplete understanding of disease natural history, identifying concepts of interest for meaningful treatment benefit given patient heterogeneity, access to patients and caregivers, concept saturation, psychometric validation, and linguistic validation when developing or adapting an instrument. As the authors point out, many of these challenges are not necessarily unique to rare disease trials, but because of the small population sizes, these challenges are magnified in rare disease research. Indeed many of the challenges under each of the roadmap headers appear to overlap quite significantly, largely driven by the issues of patient and disease heterogeneity and access to patients (small sample sizes).

Many sensible and pragmatic solutions are proposed in the report and some clear advice regarding engagement with advocacy groups is presented. However, many of these solutions appear to be based on common practices applied outside rare disease settings simply because of sample or time constraints, and there is a sense that applying the structure of the roadmap has constrained exploration of potentially novel methodological approaches. There may be benefit in thinking more broadly and creatively about alternative methods of demonstrating treatment benefit or capturing COA data in rare diseases in which the sample sizes may render more traditional statistical approaches difficult to interpret or inappropriate. Extending this consideration of methodological approaches to define benefit or value to the economic or value assessment domain may assist with the need for more creative thinking and would also be a good next step for this task force.

Other solutions presented in the report appear to rely on sample sizes that may be problematic in rare disease, such as conducting sensitivity analysis, stratifying samples by prognostic factors, or increasing the amount of qualitative work to support quantitative outcomes. The authors are very clear from the outset that these proposed solutions are not a "one size fits all" for rare disease clinical trials. These examples may be clear cases of this, but some of the suggested solutions actually raise interesting questions that would be worthwhile exploring in further work from this task force. For example, the suggestions to consider individualized outcomes or to use multiple versions of a patient-reported outcome with similar concepts are both likely to bring additional challenges (both conceptually and statistically), but would be worth considering further in our

efforts to identify a meaningful end point when the sample is very heterogeneous.

In conclusion, the work of the task force to highlight challenges and start to explore solutions associated with COAs in rare diseases is essential to ensuring that relevant and meaningful patient outcomes are adequately captured in clinical trials of rare disease. The current report provides a comprehensive account of challenges related to clinical trial end points and offers numerous suggested solutions to these challenges. Extending this work to include a deeper exploration of some methodological options and statistical approaches that also incorporates the economic/payer needs would result in a broader consideration of measuring benefit in rare disease and may also lead to novel approaches to COA or benefit measurement that may further address the challenges raised.

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REFERENCES

[1] Benjamin K, Vernon MK, Patrick DL, et al. Clinical outcome assessment (COA) in rare disease clinical trials: an ISPOR COA Emerging Good Practices Task Force Report. Value Health 2017.
[2] Food and Drug Administration. Guidance for Industry and FDA Staff Qualification Process for Drug Development Tools. U.S. Department of Health and Human Services. 2014 Federal Register.
[3] Food and Drug Administration, Center for Drug Evaluation and Research. Roadmap to Patient-Focused Outcome Measurement in Clinical Trials 2014: Federal Register 2014.
[4] U.S. Department of Health and Human Services, Food and Drug Administration. Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims. Federal Register 2009.
[5] EURORDIS. Factsheet – What is a rare disease? April 2007. Available at http://www.eurordis.org/sites/default/files/publications/Fact_Sheet_RD.pdf.