Guidance for Using Outcomes Research in Clinical Trials for Rare Diseases: Summary of the ISPOR COA Emerging Good Practices Task Force

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One of the most exciting developments in medicine in the last decade has been the explosion of potential treatments for patients with rare diseases. Products with orphan designations in the European Union and United States alone increased 4-fold between 2002 and 2016, and the sale of drugs for orphan conditions is projected to account for more than 21% of the market worldwide in the next 5 years [1].

There are an estimated 5,000 – 8,000 rare disorders identified at this time. Although these conditions affect a very small number of people, the human and economic costs associated with them can be staggering. Approximately 6% of the world's population suffers from a rare disease with nearly 75% affecting children. Most of these rare diseases are chronic and many are life-threatening [2].

The cost of medications for these diseases is often very high. For example, the median cost per patient is approximately 5.5 times greater for rare disease indications than for non-rare disorders [2]. For this reason, it is crucial during medical product development to incorporate the patient perspective in rare disease trials. Understanding the value of these treatments to the patient is increasingly important to help payers and providers, as well as patients, make good medical decisions. Clinical outcome assessments are a critical component of treatment development.

Outcomes research in rare disease clinical trials has been hampered by diverse measurement challenges due to the small, heterogeneous, and widely dispersed nature of typical rare disease patient populations. This recently published ISPOR Clinical Outcomes Assessment Emerging Good Practices Task Force Report [3] fills a long-standing gap in guidance recommendations by providing pragmatic state-of-the-art solutions to the challenges in measuring patient-reported and observer-reported outcomes in rare disease clinical trials.

The recommendations are invaluable for identifying, adapting, and implementing these types of clinical outcome assessments. The guidance document is presented with a clear recognition of the global regulatory context used in clinical development programs for rare diseases.

This report follows the US Food & Drug Administration *Roadmap to Patient-Focused Outcome Measurement in Clinical Trials*. The roadmap identifies 3 parts to successful implementation of measuring these outcomes in clinical research: 1) understanding the disease or condition, 2) conceptualizing treatment benefit, and 3) selecting / developing the outcome measure. There are significant challenges to each of these factors in studies of rare disease populations. Factors such as incomplete natural history data and heterogeneity of disease presentation and patient experience may hamper understanding the disease or condition. In such situations, the task force suggests a number of solutions including using a variety of information sources (e.g., clinical experts, patient advocacy groups, real-world data, etc.) to construct the condition's natural history and understand treatment patterns [3].

Challenges to conceptualizing treatment benefits specific to rare diseases include understanding and measuring treatment benefit from the patient's perspective, especially given potential variations in age or disease severity/progression within a study population. Recommended solutions include focusing on common symptoms across patient subgroups, identifying short-term outcomes, and using multiple types of clinical outcomes assessment instruments to measure the same constructs in different subgroups [3].

Challenges in selecting or developing the outcome measure are largely due to the small patient population and heterogeneity of the condition or study sample. Few disease-specific instruments for rare disorders exist. To address these gaps, the task force suggested strategies such as adapting existing instruments developed for a similar condition or that contain symptoms of importance to the rare disease patient population, or using a generic instrument validated for the context of use [3].

This expert consensus task force report was developed with input from more than 70 reviewers who submitted written comments, as well as substantive oral feedback during meeting presentations. It is the 11th ISPOR Good Practices for Outcomes Research Task Force Report that provides guidance recommendations for patient-reported outcomes and clinical outcomes assessments based on the FDA's *2009 Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims.* The next topic in this task force series is emerging good practice recommendations for performance-based outcome assessment.

References

[1] EvaluatePharma. Orphan Drug Report 2017; February 2017. http://info.evaluategroup.com/rs/607-YGS-364/images/EPOD17.pdf [2] EMA (a). Medicines for rare diseases. May 2016. Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/special_topics/general/general_content_000034.jsp. [3] Benjamin K, Vernon MK, Patrick DL et al. Patient Reported Outcome and Observer Reported Outcome Assessment in Rare Disease Clinical Trials - Emerging Good Practices: An ISPOR COA Emerging Good Practices Report. Value Health 2017;(7):838-855. http://www.ispor.org/valueinhealth_index.asp ■

Additional information:

To learn more about the task force, go to https://www.ispor.org/TaskForces/ClinicalOutcomesAssessment-RareDisease-ClinicalTrials.asp