VALUE IN HEALTH 20 (2017) 838–855

Available online at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/jval

# Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report

*Katy Benjamin, PhD, SM*[1,*], *Margaret K. Vernon, PhD*[2,*], *Donald L. Patrick, PhD, MSPH*[3], *Eleanor Perfetto, PhD, MS*[4], *Sandra Nestler-Parr, PhD, MSc, MPhil*[5], *Laurie Burke, RPh, MPH*[6]

[1]*ICON Commercialisation and Outcomes, Gaithersburg, MD, USA;* [2]*Evidera – Evidence, Value & Access by PPD, Bethesda, MD, USA;* [3]*Department of Health Services, University of Washington, Seattle, WA, USA;* [4]*Pharmaceutical Health Services Research, School of Pharmacy, University of Maryland, Baltimore, MD, USA;* [5]*Director, RareAccess Ltd., London, UK;* [6]*School of Pharmacy, University of Maryland, Royal Oak, MD, USA*

ABSTRACT

**Background:** Rare diseases (RDs) affect a small number of people within a population. About 5000 to 8000 distinct RDs have been identified, with an estimated 6% to 8% of people worldwide suffering from an RD. Approximately 75% of RDs affect children. Frequently, these conditions are heterogeneous; many are progressive. Regulatory incentives have increased orphan drug designations and approvals. **Objective:** To develop emerging good practices for RD outcomes research addressing the challenges inherent in identifying, selecting, developing, adapting, and implementing patient-reported outcome (PRO) and observer-reported outcome (ObsRO) assessments for use in RD clinical trials. **Good Practices for Outcomes Research:** This report outlines the challenges and potential solutions in determining clinical outcomes for RD trials. It follows the US Food and Drug Administration Roadmap to Patient-Focused Outcome Measurement in Clinical Trials. The Roadmap consists of three columns: 1) Understanding the Disease or Condition, 2) Conceptualizing Treatment Benefit, and 3) Selecting/Developing the Outcome Measure. Challenges in column 1 include factors such as incomplete natural history data and heterogeneity of disease presentation and patient experience. Solutions include using several information sources, for example, clinical experts and patient advocacy groups, to construct the condition's natural history and understand treatment patterns. Challenges in column 2 include understanding and measuring treatment benefit from the patient's perspective, especially given challenges in defining the context of use such as variations in age or disease severity/progression. Solutions include focusing on common symptoms across patient subgroups, identifying short-term outcomes, and using multiple types of COA instruments to measure the same constructs. Challenges in column 3 center around the small patient population and heterogeneity of the condition or study sample. Few disease-specific instruments for RDs exist. Strategies include adapting existing instruments developed for a similar condition or that contain symptoms of importance to the RD patient population, or using a generic instrument validated for the context of use. **Conclusions:** This report provides state-of-the-art solutions to patient-reported outcome (PRO) and observer-reported outcome (ObsRO) assessments challenges in clinical trials of patients with RDs. These recommended solutions are both pragmatic and creative and posed with clear recognition of the global regulatory context used in RD clinical development programs.

***Keywords:*** rare diseases, clinical outcomes assessment, instrument development, clinical trials.



## Introduction

A rare disease (RD) is a condition that affects only a small number of people within a population. Although no universally accepted terminology and definition have emerged to describe an RD, definitions are predominantly based on the disease prevalence within a specific country or geographical region [1]. For the purpose of this report, the term RD is used throughout, and the commonly used prevalence-based definition for an RD as a condition affecting less than 1 in every 2000 persons [2] has been adopted. The term RD in this report covers all types of diseases below this prevalence threshold regardless of their etiology, symptoms, or age of onset. No distinction is made between rare and ultrarare diseases because the concepts discussed apply equally to both. In the United States, a disease is considered rare if it affects fewer than 200,000 persons [3], and the European Union defines an RD as a condition with a prevalence of less than 1 in every 2000 persons [2]. Other regions use different definitions [1]. These conditions are often referred to as "orphan" diseases because traditionally they have not been "adopted" by the

Co-chairs of this effort: Katy Benjamin and Margaret K. Vernon represent the ISPOR Rare Disease Clinical Outcomes Assessment Task Force (https://www.ispor.org/TaskForces/ClinicalOutcomesAssessment-RareDisease-ClinicalTrials.asp).

* *Address correspondence to*: Katy Benjamin, ICON Commercialisation and Outcomes, 820 W. Diamond Avenue, Gaithersburg, MD 20878.
*E-mail addresses:* katy.benjamin@iconplc.com; margaret.vernon@evidera.com

1098-3015$36.00 – see front matter © 2017 Published by Elsevier Inc. on behalf of International Society for Pharmacoeconomics and Outcomes Research (ISPOR).
http://dx.doi.org/10.1016/j.jval.2017.05.015

**Background to the Task Force**

Since 2009, ISPOR has published 10 ISPOR Clinical Outcomes Assessment (COA) Good Practices for Outcomes Research Task Force Reports (https://www.ispor.org/workpaper/practices_index.asp). They address aspects of the development and application of COAs, defined as any reported assessment used to support primary or secondary endpoints to document treatment benefit. These reports are consistent with the US Food and Drug Administration's guidance for industry, "Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims" that described how the FDA would evaluate the adequacy and appropriateness of PRO measures used as effectiveness end points in clinical trials.

With the increased attention on rare diseases and the orphan drugs that treat them, the task force wanted to address outcomes measurement in rare disease (RD) clinical trials. In October 2013, the ISPOR Health Science Policy Council accepted the task force proposal recommending the formation of an Emerging Good Practices for Outcomes Research Task Force on patient-reported outcome (PRO) and observer-reported outcome assessment in rare disease trials. The ISPOR Board of Directors subsequently approved the task force.

The task force was comprised of experts in PRO and other outcome assessment development, psychometrics, clinical trial data collection, and regulatory affairs. They represented a range of perspectives, including government (US FDA), academia, research organizations, and the patient engagement and rare disease community. The report was reviewed twice with 70+ ISPOR member reviewers around the world submitting written comments. In addition, the task force received oral feedback at four ISPOR International Meetings and European Congress presentations. This valuable and constructive feedback contributed to an expert consensus emerging good practices task force report. ISPOR members submitting written comments are listed by name in the report's acknowledgements section.

pharmaceutical industry, where the small market has provided little incentive to develop new treatments [4]. Throughout this report they will be referred to as "rare diseases or conditions," to differentiate them from subgroups of patients with more common conditions who may benefit from "orphan" treatments.

RDs represent a wide variety of disorders and constellations of clinical signs and symptoms. Many are catastrophic, causing chronic or progressive physical degeneration, disability, or premature death. At present, most are incurable. An estimated 80% have a genetic etiology. Approximately 75% of RDs affect children, and 30% of these children do not live to age 5 years [5]. Between 5000 and 8000 distinct RDs have currently been identified; on average, five new RDs are described every week in the medical literature [6]. Although few patients have any specific RD, between 6% and 8% of people worldwide are estimated to be affected by an RD [6]. Approximately 30 million people in the United States and another 30 million in the European Union are reported to suffer from a rare condition [7].

Correct diagnosis of an RD is often delayed by many years because of lack of health care providers with relevant clinical training and experience in recognizing and treating these disorders [8]. Few treatment options are available for many RDs, and appropriate treatments, if they exist, can be difficult to access [8] and are very costly [9,10]. As a result of these two factors, patients with RDs typically have many unmet medical needs.

In the last few decades, legislation and other factors have stimulated research, development, and marketing of targeted medications for RDs that would otherwise not have been profitable for drug manufacturers. The introduction of orphan drug legislation, such as the Orphan Drug Act in the United States in 1983 [11] and the European Union Regulation on Orphan Medicines in 2000 [3], has been key to spurring the development of orphan drugs, defined as "medicinal products intended for diagnosis, prevention or treatment of life-threatening or debilitating rare diseases" [12]. Since the adoption of orphan drug legislation, the US Food and Drug Administration (FDA) has approved 600 drugs for rare conditions [13] and the European Medicines Agency has approved 128 drugs [14]. The number of orphan drug designations and approvals is rising, and orphan drugs are predicted to account for just over 20% of all prescription drug sales by 2020 [10].

Development of medical treatments for RDs has also been stimulated by a number of legal and financial incentives, national rare disease policies, and accelerated drug evaluation schemes. Improved genetic and molecular understanding of disease mechanisms and scientific, translational, and technological advances have led to a surge in new RD treatments [15]. The rise of RD patient advocacy organizations (PAOs) has also played a part in the increase in RD treatments, fostering greater awareness of the public and the scientific community regarding the paucity of effective treatments for these conditions. Many PAOs support the use of patient-centered outcome measures to assess treatment benefit in RD clinical trials.

A position paper by the European Organisation for Rare Disorders (EURORDIS) emphasized the need to assess treatments from the patient perspective, especially in terms of impact on patients' daily lives and functioning [16]. Patients' quality of life was listed as a major priority for RD research [17]. To further this agenda item, EURORDIS called for developing and validating patient-reported outcome (PRO) tools to support evidence of treatment benefit, as well as increased funding for research on patient quality of life and a patient-centered approach to care [16]. Similarly, in 2015, the US Congress directed the Secretary of Health and Human Services to implement within the FDA a program of patient-focused drug development with a structured risk-benefit framework to facilitate in order to understanding of the balance of risk and benefits in new drug development to aid in regulatory decision making and the communication of risks and benefits of new drugs. The approach highlighted the importance of the patient voice in this process by mandating that "patient experience data" be the central mechanism for understanding and interpreting treatment risk-benefit [18].

The growing focus on RD medical treatments is complemented by increasing efforts to include the patient perspective in all areas of medical research, including the evaluation of medical product efficacy. Evaluating the efficacy and safety of RD medical treatments from the patient's perspective is considered necessary to understand how to improve patient care and well-being and to provide information that will be meaningful to patients and allow them to select the treatments most appropriate for their condition [19]. Although payer concerns are beyond the scope of these recommendations, it should be noted that the high cost of many new treatments for RDs also requires a high level of proof of treatment benefit that can be addressed by evidence of improvements that are meaningful to the patient. Increasingly, regulatory bodies are including evidence of the patient perspective in their decisions. For example, the goal of the FDA Clinical Outcomes Assessment (COA) staff (formerly a part of the FDA Study Endpoints and Labeling Development staff) is to ensure that meaningful medical product information is available to health care providers, caregivers, patients, and families through the advancement of innovation and excellence in clinical trial measurement of treatment benefit. Issues and challenges generic to the development or selection of COA measures are described in many other regulatory guidance