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

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### 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.

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### 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>).

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## 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\\_in\\_dex.asp](https://www.ispor.org/workpaper/practices_in_dex.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

documents including the European Medicines Agency Guideline on Clinical Trials in Small Populations in 2006 [20].

The European Medicines Agency has also developed a draft reflection paper on the measurement of PROs in oncology studies [21]. Other organizations have proposed standards for the development, assessment, and analysis of PRO measures in general, including the Consolidated Standards of Reporting Trials, the International Society for Quality of Life Research, and the Consensus-based Standards for the Selection of Health Measurement Instruments.

Patient-centered outcomes are defined as “those outcomes important to patients’ survival, function, or feelings as identified or affirmed by the patients themselves, or judged to be in patients’ best interests by providers and caregivers when patients cannot report for themselves” [22]. There are significant challenges to developing, modifying, or selecting outcome assessments for the evaluation of RD treatments. Although these challenges may also apply to nonrare conditions, they tend to be magnified in RDs because of the small size of patient populations. Challenges that are typical when working in RDs include the following:

1. Heterogeneity of disease presentation, course, and response to treatment within individual diseases;
2. Unknown or incomplete disease natural history;
3. The large number of RDs that affect vulnerable populations, especially young children; and
4. RDs may be associated with significant, often progressive, disability and cognitive impairments [23].

These challenges make it more difficult to obtain relevant, valid, and reliable information about the patients’ experiences with their condition and the treatment under consideration.

The debilitating, often progressive nature of many RDs, the young age of many patient populations with RDs, and the cognitive or physical impairments associated with many of these conditions may pose challenges to collecting data on treatment benefits directly from patients in the form of PRO measures. Thus, although the collection of PROs in RD studies may be desired, this may not always be practical. If patients are unable to self-report on their disease experience, it will be necessary to collect information regarding treatment benefit indirectly from clinicians, parents, or others who have direct knowledge about patient condition-related behavior, signs and symptoms, or functional status. In such cases, indirect measures of treatment benefit may be required on the basis of patient observation, that is, observer-reported outcomes (ObsROs) or clinician-reported outcomes (ClinROs). Please see ISPOR’s 2017 task force report on ClinRO assessments of treatment benefit for details [1]. Measures of clinic-based performance outcomes (PerFOs) may also provide efficacy evidence related to motor, sensory, or cognitive status. This report focuses on PRO and ObsRO COA measures.

## Task Force Objective and Scope

The task force’s objective was to describe emerging good research practice recommendations for addressing the challenges inherent in identifying, selecting, developing, adapting, and implementing PRO and ObsRO assessments for use in clinical trials of RDs.

The task force coauthors note here and emphasize throughout this article the following:

1. Each RD drug-development program will present its own unique challenges to selecting and/or developing and implementing COAs.

2. There is no single solution for addressing the myriad and diverse difficulties that may arise with the development and implementation of these measures, and the development of evidence to support their use within various RD contexts of use.
3. This article presents possible solutions to address common obstacles that arise when working in RD populations. Not all solutions will be appropriate or pragmatic for every context of use (COU).
4. Within any specific RD drug-development program, innovation, creativity, and flexibility will be required on the part of investigators to optimize outcome selection, evidence development, and study design.
5. This report is concerned with the challenges specific to or magnified by developing or modifying COAs in the context of RD clinical trials. It does not discuss considerations relating to clinical trial design, or the suitability of these measures to inform cost-effectiveness, value assessments, health technology assessments, and/or payer decisions.

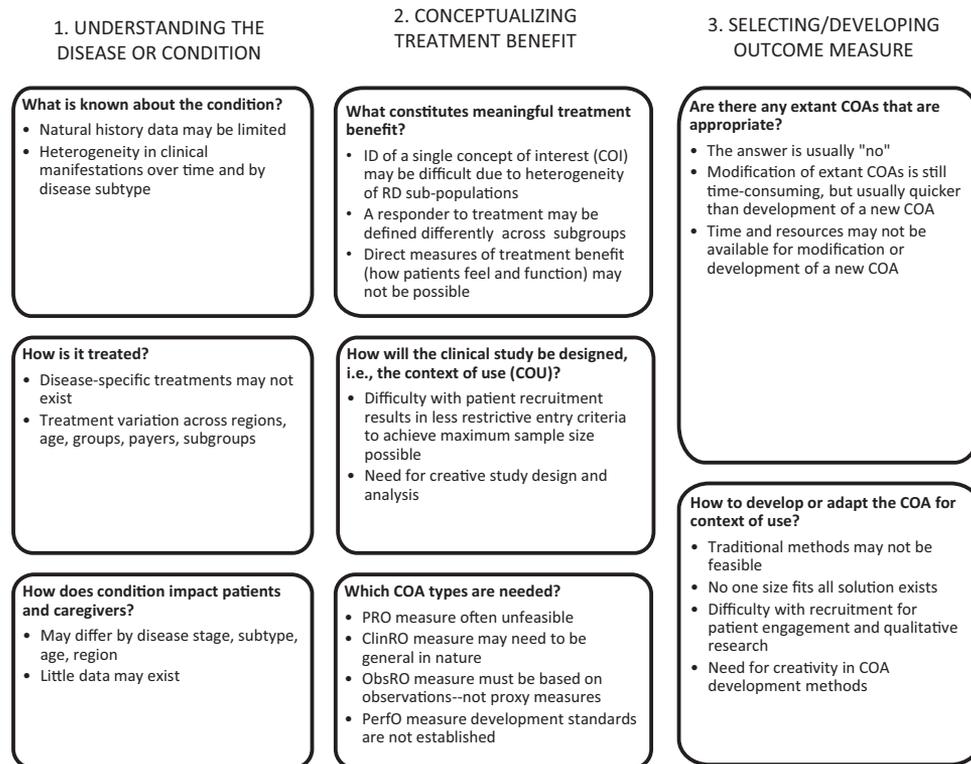
Although there are considerable obstacles to implementing COAs in clinical trials of treatments for RD populations, some suggested solutions and methodological innovations have been proposed [19,24–26]. Where feasible, resources/references are included to provide recommended approaches to identifying, adapting, or developing COAs for RDs.

In summary, standard methods and strategies of COA identification, development, validation, and implementation, including those recommended by regulators, *need to be operationalized in the context of the special challenges associated with RD populations*. This article provides emerging good practices for adapting such methods and strategies in light of these challenges. The concepts and practices outlined in this article can be considered a starting point for future empirical research to build a set of valid, scientifically sound, and accepted best practice standards for capturing the patient perspective in RD studies.

## Structure of the Task Force Report

Measuring how patients survive, feel, and function is an integral component of the development, review, and regulation of new treatments. The FDA has developed and implemented standards for COAs used as effectiveness end points [27]. As part of this effort, the FDA has published a Roadmap to Patient-Focused Outcome Measurement in Clinical Trials [28] (see Appendix 1, heretofore referred to as the Roadmap, in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2017.05.015>) to assist medical product developers in thinking about and identifying the optimal COAs for use in clinical trials. The Roadmap outlines each step in the process for understanding the effects of a treatment, taking into account the condition of interest and the desired outcomes from the patient perspective, and incorporating this knowledge into the selection, adaptation, or development of appropriate end points reflective of outcomes meaningful and important to patients. The Roadmap can be applied to determination of either disease-specific or generic outcome measures as potential COAs in RD trials, provided their validity and responsiveness for the intervention and in the context in question have been demonstrated in accordance with good research practices.

The organization of this article draws from the FDA COA Roadmap, using this as a framework to discuss the challenges that arise in COA identification, modification, development, and implementation in RDs according to each Roadmap column (see Fig. 1). Examples are provided to illustrate the RD-specific challenges associated with each column. Potential solutions are suggested to guide investigators through the process of choosing measures that are appropriate for the given COU and for



**Fig. 1 – Challenges for Implementing COA Endpoints in Rare Disease Clinical Trials. \*Adapted from Food and Drug Administration [28].**

developing the evidence of the instrument's validity and reliability necessary to support these end points within the context of an RD clinical trial.

#### Column 1: Understanding the disease or condition

Typically in COA instrument selection or development, an understanding of the natural history of disease and relevant patient-centered outcome concepts is obtained through review of the literature, expert clinician interviews, qualitative interviews with patients and/or their caregivers, or surveys of patients or caregivers. However, sufficient understanding of natural history in RDs may be hampered by several factors.

There are often large knowledge gaps in the etiology of RDs. This problem may be compounded by variations in disease genotype and/or phenotype. It is estimated that about 80% of RDs have a genetic etiology, frequently with multiple phenotypes [29]. Depending on the mutation, sex, and other factors, patients with the same diagnosis can experience disease manifestations ranging from severe, rapidly progressive forms that often present in early childhood to types that progress slowly and that may not become apparent until adulthood. A related problem is that patients with RDs are frequently misdiagnosed or undiagnosed for a significant time after the first symptoms appear; recent studies have found an average time to diagnosis anywhere from 15 months to 28 years [17,30,31]. Thus, the early stages of these conditions may not be completely understood and the full spectrum of symptoms and clinical manifestations of an individual with a consequent lack of disease awareness or complete understanding in the medical community. Adding to this lack of clarity, patients may have received inappropriate treatments because of misdiagnosis; any iatrogenic impacts are usually unknown and could be difficult to separate from the RD symptoms.

Complete understanding of the RD can also be difficult to achieve because, given the variations in disease, different treatment goals or clinical assessments may be more appropriate for one subpopulation versus another. For example, osteogenesis imperfecta is a heterogeneous group of inherited connective tissue diseases defined clinically by excessive skeletal fragility and recurrent fracture. There are four main types, with severities ranging from lethal at birth to minimally symptomatic cases often not recognized until adulthood. Although the main clinical manifestation is bone fracture, other common symptoms are abnormal dentition, joint laxity, hearing loss, ocular disease, respiratory problems, and vascular and valvular heart disease. Some patients may experience severe skeletal and facial deformities or become increasingly physically disabled, whereas others have very slight physical or functional impairments [32].

Conversely, although subtype variations in a single RD can lead to different diagnoses and treatments, another common scenario in RDs is that a group of diseases may be clustered into a single syndrome on the basis of similarities in clinical manifestations, although they are actually different conditions with important differences in their genetic origins, symptom profiles, and patient experience of disease. For example, Batten disease, a progressive neurodegenerative disorder, is actually several different conditions caused by one of at least eight different genetic mutations in the neuronal ceroid lipofuscinose gene. Although the individual disorders have similarities in their clinical manifestations, notably progressive neurocognitive impairment, there are also important differences between them that have significant diagnostic, prognostic, and treatment implications [33].

There may also be only a small number of patients and caregivers available to participate in qualitative studies to understand the patient experience, and those who are included may not represent the full spectrum of disease manifestations. In

combination with the knowledge gaps in etiology and natural history data and variations in disease manifestations, it can be difficult to develop a complete understanding of the relevant disease experiences and important outcome concepts.

A careful description of the full range of the clinical manifestations, timelines for disease progression, and clinical outcomes for the different phenotypes is extremely important to assess and select outcome measures that are meaningful to patients with different disease subtypes or at different stages of their condition. Without sufficient available information on the disease or condition (column 1), it can be difficult to conceptualize treatment benefit, to design a clinical study to test those benefits (column 2), and to select or develop the appropriate outcome measure to evaluate these benefits (column 3). Various information sources may be necessary to fully understand the disease or condition and to construct an appropriate COA measurement strategy.

Table 1 provides a summary of potentially available data sources to evaluate and review when developing an understanding of RDs with limited natural history data. The difficulties associated with understanding rare conditions and their treatments are listed in the first column, and the potential solutions are presented as column headings. Check marks in individual cells indicate a potential solution relevant to a specific obstacle. Note that we refer to these data sources in a general sense and each should be assessed as to whether they are fit for purpose. For example, social media presents a burgeoning but wide range of possibilities and although it can be an informative channel for qualitative studies, it is fraught with its own challenges.

The following sections provide further details regarding RD challenges and approaches for each aspect of understanding the natural history, health care environment, and patient perspectives for specific RDs.

**1A. Challenge: An Incomplete Understanding of the Disease Natural History.** This poses challenges for COA selection, development, and/or implementation because the relevant concepts of interest are not completely apparent without this information. Although this limitation is also a concern for non-RDs, the newness of many recently described RDs, along with the small patient populations, disease subtypes, heterogeneity of severity, symptoms and disease progression, as well as the frequently lengthy time to get a correct diagnosis make this especially problematic for these conditions.

#### Suggested Solutions

- 1A.i. Use all available sources of information to understand natural history, including observational studies and registries, published and anecdotal case reports, opinion of clinical experts, and literature reviews as well as patient journey interviews with patients and caregivers. These sources can be starting points for building a disease knowledge base, and can help to identify basic features of the disease, distinctions between different genotypes/phenotypes, prevalence, and any geographic clustering of disease subtypes or treatment patterns. Note that case reports may be the only publications in RDs that describe patients' symptoms and experiences. Although they cannot be assumed to be representative of the entire target population, they can be useful to obtain an initial understanding of the condition that can be used to develop qualitative patient, caregiver, or clinical expert interview studies. It can also be useful to review medical records and administrative or billing (reimbursement) data to understand treatment patterns, as well as any relevant country or region-specific policies on access to

care or other health-related services, disability-related policies, and so forth.

- 1A.ii. The RD community is highly motivated to advance science, research, and patient care practices. Engaging with RD patient advocacy organizations (PAOs) to recruit patients for natural history studies and patient journey studies (describing the patient experience with disease and treatment) or disease registries can ensure the long-term viability of these studies and is strongly encouraged. Consider working with patient groups to develop surveys or registries that patients can access via the Internet globally to submit their data.
- 1A.iii. Given the diagnostic delay associated with many RDs, it may be especially important to understand the time frame from first disease symptoms to correct diagnosis and treatment in order to enable distinctions between RD-related symptoms and impacts and those due to iatrogenic conditions. This may also provide information on time to progression.

**1B. Challenge: Diversity in Disease Presentation (Heterogeneity) and Patient Experience.** There can be substantial heterogeneity in RDs, both between and within disorders. For various reasons (Table 2), this heterogeneity can result in a wide diversity in initial presentation, clinical manifestation, and progression of the disease between patients with the same underlying condition. There can also be regional and cultural differences in how the RD is perceived and treated, leading to different perspectives within a single RD patient population regarding what constitutes a meaningful treatment outcome. These factors pose unique challenges to identifying the most appropriate patient-centered concepts of interest (COI) and parameters for measurement of the treatment outcomes most salient and important to all patients.

#### Suggested Solutions

- 1B.i. Where possible, focus on the most common symptoms and impacts of the condition of interest that are most important to patients (and/or caregivers) and would be expected to improve or stabilize with treatment given the therapy's (hypothesized) treatment effects and target product profile as per the COU.
- 1B.ii. To identify and focus on the most prevalent and important symptoms and impacts of the condition, the following recommendations may be helpful:
  - a. Develop an understanding of the disease natural history using all available sources of information (see column 1, challenge 1).
  - b. Conduct concept elicitation (CE) interviews with patients and/or caregivers and clinicians to understand disease experience over time. When gathering data from patients and caregivers, obtain information about patient treatment and clinical management history. This will be helpful in differentiating signs/symptoms of disease from those due to other causes.

If possible, select a range of patients and caregivers representative of various ages, disease stages or subtypes, and relevant national or demographic subgroups to ascertain differences and commonalities in terms of how the RD is experienced, the importance and impact of symptoms, and societal perceptions of/reactions to the condition.

- 1B.iii. To understand how regional diversity may impact RD presentation, the following suggestions may be helpful:
  - a. Engage patients and clinical experts from different

**Table 1 – Data sources used to develop and understand RDs.**

Challenges	Local policies & regulations	Literature*	Existing data (claims, clinical trials, electronic medical records/ electronic health records)	Expert clinician interviews	Social media	Patient/ caregiver interviews, surveys	Observational studies, registries	Patient advocacy groups
<b>1A. Incomplete understanding of the natural history</b> o Misdiagnoses/inappropriate treatments o Difficulty distinguishing between RD signs and symptoms and those due to the consequences of inappropriate treatments o Varying time to diagnosis o Regional treatment variations o Diversity in disease presentation	✓	✓	✓	✓	✓	✓	✓	✓
<b>1B. Diversity in disease presentation (heterogeneity) and patient experience</b> <b>Unknown subpopulation factors</b> o Highly heterogeneous disease manifestations o Unknown range of severities along disease trajectory o Disease variations caused by unknown factors <b>Varied health care environments</b> o Variation across nations and regions o Lack of standards of care or disease management guidelines <b>Variable patient, caregiver perspectives</b> o Regional difference in meaning and awareness of RDs o Regional difference in definition of treatment benefit and acceptable risk o Regional difference in perceived burden of disease	✓	✓	✓	✓	✓	✓	✓	✓
<b>1C. Barriers to obtaining input of patients and caregivers</b> o Wide dispersion of patient population o Competition for participation in multiple studies o Study participation fatigue o Ethical considerations		✓	✓		✓	✓	✓	✓

\* Not restricted to peer-reviewed literature.

**Table 2 – Reasons for diversity in RD presentation.**

Reason for diversity	Consequences of diversity
Phenotypic diversity	<ul style="list-style-type: none"> <li>• Variations in treatment effectiveness</li> <li>• Variations in the type, timing, and severity of symptoms for patients with the same underlying disease [58]</li> </ul>
Disease progression	<ul style="list-style-type: none"> <li>• Core signs and symptoms of the disease may not be stable over course of disease</li> </ul>
Delayed diagnosis	<ul style="list-style-type: none"> <li>• Variations in types and patterns of treatments</li> <li>• Variations in disease trajectory due to differences in disease progression</li> </ul>
Incorrect diagnosis	<ul style="list-style-type: none"> <li>• May result in inappropriate treatments</li> <li>• May result in iatrogenic illness</li> <li>• Signs/symptoms associated with inappropriate treatment can be hard to distinguish from the RD itself</li> <li>• May change trajectory of RD</li> </ul>
Few standards of care	<ul style="list-style-type: none"> <li>• Variations in treatment patterns by geography or payer</li> <li>• Variations in patient health status, treatment outcomes</li> </ul>
Regional and cultural differences in meaning, significance of RDs	<ul style="list-style-type: none"> <li>• Patient perception of disease experience may differ on the basis of geography, culture, clinical management, significant life events</li> </ul>
RDs, rare diseases.	

regions with knowledge and relevant experience in diagnosis and treatment of the specific RD to understand geographic differences in patient characteristics, disease management strategies, and patient experience.

- b. Other data sources such as registries or national surveys, claims databases, electronic medical record reviews, and specific payer policies or decisions can also be helpful in understanding geographic variations in patient experience, standards of care, access to clinical expertise or effective treatments, optimal clinical management, and so forth.
  - c. Work with local patients and PAOs to obtain a representative picture of treatment patterns, from first symptoms to definitive diagnosis and beyond, and to understand the patient experience throughout this trajectory. Be sure to consider that the sample is potentially biased in that patients who are motivated to join PAOs or online communities may be different from those who do not.
- 1B.iv. It is also useful to understand the consequences of diagnostic delays on patient outcomes. Those diagnosed early in their illness may have a longer time to disease progression, fewer or less severe symptoms, and lower risk of iatrogenic illnesses. Obtaining information about time from first symptoms to correct diagnosis and treatment received is important when developing the conceptual model of disease and subsequent COA measurement strategy.

**1C. Challenge: Barriers to Obtaining Input of Patients and Caregivers.** Because of the rarity of the condition, it can be difficult to identify patients and caregivers for engagement in COA instrument validation or development studies. The small size of the patient population usually implies a lack of geographic concentration, making participation in these activities difficult; specifically, it may be challenging to organize focus groups or to conduct face-to-face interviews in an efficient manner. The wide dispersion of cases can magnify the usual practical considerations involved in study participation, (e.g., transportation, need to modify work or treatment schedules, and finding time away from caregiving to participate), which can also influence a patient's or family's ability and willingness to participate in an interview or focus group, especially given the large number of RDs that affect children. Moreover, as the number of new potential treatments for RDs increases, there is a danger of participant fatigue, especially where patient populations are very small, and there

is competition for their participation in multiple studies. Furthermore, researchers may be viewed with some suspicion in terms of their motives. Thus, in designing COA development studies, researchers must be sensitive to these issues [34].

#### Suggested Solutions

- 1C.i. Where they exist, partner with a PAO to design the study as well as to support patient recruitment efforts. PAOs can frequently broker relationships between researchers and patient communities, either directly or through their work with clinicians. However, negotiating this relationship can be a sensitive proposition. Several strategies may help to overcome PAO's potential concerns and help to ensure a successful research partnership:
  - a. Before contacting a potential PAO, get to know the organization and understand its focus and scope. Does the PAO have direct access to patients? Is there a focus on working with researchers and assisting with study design, recruitment, and so forth, or is the organization largely focused on supporting families and patients in finding clinical care resources, or providing a platform for the patient community to exchange experiences and information? Do they have a well-defined social media presence? Do they work with an existing umbrella organization? Do they have their own research network and studies that are closed to outside projects? All these factors may have an impact on a PAO's ability and willingness to support patient engagement and mobilization for participation in research initiatives.
  - b. Partner with the PAO in designing the study and study materials (e.g., interview guides, protocols, and recruitment messages) or reporting study results. This can increase patient or caregiver buy-in and commitment to the research project and will ensure that the study is relevant and appropriate for the target population. There are a number of resources to identify potential PAO partners. The OrphanNet Web site includes a comprehensive list of PAOs, searchable by disease. Other resources for identifying potential PAO research partners include RareDiseases.org, EURORDIS, and the National Organization for Rare Diseases.
  - c. If there is an umbrella organization for the RD community of interest, it may be useful to contact this group

first before attempting to directly contact a specific local PAO. The umbrella organization typically has good contact with local organizations, which can be quite small. They also may have more resources and can help communicate with members through email blasts, social media, and so forth. The umbrella organization can provide guidance on which PAOs are best suited for research purposes, training, and support.

- d. Umbrella organizations can also assist in brokering the relationship between the research team and the local PAOs. However, it is worthwhile to do some investigation of the organizations, their relationships, and interactions before working with them. Although working with umbrella groups can be very useful, it should be approached with caution. Not all smaller PAOs have collaborative relationships with their larger counterparts. Be cognizant of the nature and quality of these relationships before contacting a PAO.
  - e. It should be noted that many pharmaceutical companies developing products for RD indications have one or more specifically designated liaisons responsible for engagement with patients and/or patient groups. If the COA development study is conducted with a pharmaceutical sponsor, a designated individual within the sponsor organization will engage patients and/or groups as the company's established point of contact and relationship manager. Often, company staff is required to work through this established relationship manager and cannot reach out to patient groups directly. Researchers should work with these designated liaisons to avoid confusion and to ensure relationships are clear between the researchers, company, and the POA.
- 1C.ii. If conducting face-to-face interviews with patients and caregivers is difficult, data collection via telephone interviews and surveys may offer potential alternatives.
  - 1C.iii. Consider collecting data using Internet-based resources. Analysis of relevant social media blogs or "member stories" can enrich understanding of the patient or caregiver experience, and provide a deeper and more comprehensive picture of patients across geographic regions or demographic characteristics than would be possible in a small qualitative study. Sites such as RareConnect.org or PatientsLikeMe provide a joint platform for RD communities from different geographies and may contain a wealth of patient and caregiver comments and information. Before implementing such a strategy it is advised to contact the site sponsor or community site moderator to alert them to your presence and purpose, and to confirm that there are no restrictions on these activities by a nonpatient participant because your actions may otherwise be considered an intrusion.

Note that a limitation of these forums is that there is no independent clinical verification of the information provided by the participating individuals and no method of confirming the RD diagnosis they claim to have. Furthermore, the Internet access, motivation to blog or communicate in an open forum, and technical ability these individuals possess may not be typical of most patients, and certain experiences may be modified or altogether absent depending on the needs and circumstances of the writer. Thus, data based on this source of information cannot be considered representative of all patients, or all patient experiences, with the RD. However, these sources can be helpful in generating a hypothesis and informing future, targeted research with patients with a confirmed diagnosis and known clinical characteristics. Also consider other Internet and technology-based sources such

as health apps developed to capture patient health-related experiences or electronic health records that capture patient-reported outcomes data.

Be cautious regarding the anonymity of Internet posts among small populations. It may be difficult to keep data completely anonymous because 1) in a ultrarare disease it could be obvious as patients are a small handful of individuals and 2) when publishing, excerpts can be readily "searched" online and linked to identifiable blogs.

- 1C.iv. Partner with an expert center or dedicated clinical care network to identify and recruit potential participants for qualitative research studies. Such organizations can have access to patients beyond their geographic region because the lack of local clinical expertise often results in the need for patients to travel to obtain needed care. Again, organizations such as Orphanet, EURORDIS, and the National Organization for Rare Diseases, virtual and actual clinical centers of excellence such as the European Reference Network for rare diseases, and individual RD-specific patient advocacy organizations (PAOs) often include information about RD-specific clinical centers and clinical experts that can be used to identify these resources. Another useful way to identify clinics and clinicians with expertise in treating the RD of interest is through the pharmaceutical company liaison to one of these clinical groups.
- 1C.v. Consider partnerships among multiple biopharmaceutical companies with clinical development programs in the specific patient population. This can reduce the impact on the limited patient population, and can be coordinated (if willing) through a PAO. At a precompetitive point and with a spirit of data sharing this can be both a practical and ethical solution, and can avoid repeated sampling of small populations.

#### *Column 2: Challenges and solutions: Conceptualizing treatment benefit and the measurement context*

To generate meaningful information about treatment benefit, the data gathered as described in column 1 are used to conceptualize the outcomes of importance to measure the concept(s) of interest for the specific condition, patient population, and treatment COU. An adequate COA must generate a score that represents both the expected treatment effect, as stated in the clinical trial study objectives, and meaningful treatment benefit as described by patients. Establishing the COA (e.g., the identification, modification, or creation of the COA, as described in column 3) cannot take place until the study objectives related to meaningful treatment benefit are defined in the study COU.

Specific impediments to defining the COI and COU in RDs can arise from 1) lack of understanding of the natural history of the condition, 2) heterogeneity of disease presentation, and 3) incomplete understanding of treatment benefits due to difficulty in accessing patients or caregivers to provide a comprehensive perspective on the most prevalent and important signs/symptoms of the disease to assess in the clinical trial. Although all these obstacles were discussed previously under column 1, the challenges and potential solutions specific to the establishment of the COI and COU are discussed in this section as outlined in [Table 3](#).

To obtain an understanding of desired treatment benefits, disease and treatment characteristics need to be considered from the perspective of all health care decision makers, particularly patients and their caregivers. Meaningful treatment benefit common to all patients with a specific RD depend on several factors that may influence how patients experience their illness and their expectations for how a treatment can improve their condition. The low prevalence of a particular RD frequently necessitates

**Table 3 – Challenges and suggested solutions: Conceptualizing RD treatment benefit and the measurement context.**

Challenges		Focus on measurable core signs, symptoms, and impacts that are relevant across all patients	Use study population selection criteria that focus on exclusion of other diseases	Group patients by similar treatment patterns to control for regional context variations	Collect additional data on environment to ensure correct stratification parameters for analyses	Use electronic data capture to collect data across regions	Conduct concept elicitation study to evaluate differences in patient experience between disease subtypes and geographic regions
A. Identifying concept(s) of interest (COI) for meaningful treatment benefit	Highly diverse collection of disorders; clinical heterogeneity within individual disorders	✓			✓		✓
	Difficulty distinguishing RD signs and symptoms from those due to iatrogenic causes	✓	✓				✓
	Overlapping signs and symptoms with other more common conditions	✓	✓				✓
B. Define context of use (COU) for clinical trial	Variations in treatment, cultural context, and/or language across countries in multiregional studies			✓	✓	✓	✓
C. Select clinical outcome assessment type	Need to include multiple age ranges in trial and/or disease progression over time may necessitate measure adapted for self-report (PRO), observer-report (ObsRO) and clinician-report (ClinRO)	✓					✓
PRO, patient-reported outcome; RD, rare disease.							

including participants from multiple age groups and geographic regions, with various comorbidities, phenotype, or disease severity subgroups, and so forth within a clinical trial.

This can present challenges when choosing the outcome to be assessed by study end points because patients' definitions of treatment benefit and perceived outcomes can vary considerably according to illness-related cultural beliefs and attitudes, age group, treatment history and expectations, understanding of the disease and prognosis, and level of impairment [35–37]. Thus, it will be important to build on the information obtained in column 1 to plan a COA measurement strategy that addresses differences in patients' demographic characteristics, health care environment, and perceptions of treatment benefit, risk, and disease impact.

An example of the complexities involved in defining treatment benefit due to these factors can be found in amyloidosis, a condition caused by misfolded proteins that can deposit in organs and tissues, disrupting normal functioning in various systems (see Appendix 2 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2017.05.015>). In all, 28 different proteins are associated with amyloidosis, 14 of which have systemic manifestations; specific subtypes of the disorder can be found in several disparate regions, including Portugal, Sweden, Japan, Ireland, Spain, France, Finland, Germany, and Greece [38]. The rarity of this RD, estimated at approximately 20 cases/million population [39], implies the need to include a wide variety of patient subgroups in a single study although there may be only a few individuals in each subgroup. Subgroup analysis in such situations can be difficult if not impossible. Achieving concept saturation to identify the main symptom and impact themes can be similarly challenging.

Another challenge to arriving at a common conception of treatment benefit across all patients with a specific RD is the high percentage of RDs affect children in whom there are rapid and often variable cognitive and physical developmental changes both within and across age groups [40]. In such cases, it may be difficult to identify a COI that can be represented by a single COA. Where it is necessary to include a broad age range of patients in a clinical trial, it may also be necessary to include COAs that are appropriate for both younger and older children, as well as adults, in the form of different age-appropriate PROs or even PROs for older children and adults and an ObsRO for children too young to reliably self-report their RD symptoms and experiences. In such circumstances, it will be necessary to develop a measurement strategy that can collect data on the same constructs from both the patient symptom experience and the observed behaviors. Measurement strategy for progressive conditions may also need to encompass both self-report and observer- or clinician-reported outcomes to account for potential increased disability over the course of the clinical trial.

Disease progression can also influence patients' definition of desired treatment benefits across the disease continuum.

For patients, especially those earlier in the disease trajectory or with milder or less-progressed illness, with advanced disease, small improvements or even stable disease with no, or slowed, progression is a desired outcome; others may desire clear symptom improvements and better physical functioning. In the case of patients with systemic amyloidosis in which different subtypes have different kinds of organ involvement, treatment benefit may constitute very different symptom improvements for someone with cardiac involvement and someone else with liver involvement.

**1. Challenge: Identifying Concept(s) of Interest for Meaningful Treatment Benefit.** As described above, it is often difficult to ascertain a clear and consistent understanding of treatment benefit in RDs due to the heterogeneity of the condition itself as well as the wide variation in patient experiences in treatment and cultural attitudes. The small size of the target population further complicates matters because it is necessary to include

patients with a wide range of relevant characteristics such as ages, degrees of disease progression, comorbidities, and expectations for improvement in their condition.

#### Suggested Solutions

- i. Because the importance of core disease characteristics may vary by patient subgroup or change over time, conduct CE studies with as many relevant patient/caregiver groups as possible/feasible to identify those most salient to all patients. Furthermore, rely on medical experts experienced in treating patients with the disease of interest to understand relevant signs/symptoms.
- ii. Consider what the most important differentiating characteristics are in terms of disease subtypes, age group, ethnic groups, degree of progression, or other specific factors that may lead to variation in disease experience and perceived treatment benefit, based on findings in CE interviews, interviews with medical personnel, as well as the results of any natural history studies.
- iii. Consider severity, nature, timing, and degree of involvement of affected body systems based on natural history information.
- iv. Consider developing a COI definition that takes into account the important symptoms in various subtypes, with a COA strategy that includes measurement of various outcomes in a single scale or symptom battery.
- v. Ideally, end points should apply to all clinical trial participants. It is imperative then to focus on core signs, symptoms, and impacts that apply to most or all patients. If COA assessments have items or evaluations that do not apply to all, there will be missing values that may lead to masking of some treatment benefits given the already small samples.
- vi. Where application of the same COA/items across all individuals is not possible due to heterogeneity of disease presentation, individualized outcomes (outcomes that evaluate different relevant signs/symptoms for each individual and change in these specific signs/symptoms over time to evaluate treatment benefit) might need to be considered.
- vii. Given disease heterogeneity, it is probable that participants in the clinical trial will enter with different disease severities and baseline values on COA assessments. Take into account differences in severity level and starting values in determination of responder definitions used to determine treatment benefit; for example, responder definitions might be different depending on baseline status.

**2. Challenge: Understanding the Relationship between the COA and All Other Study End Points.** In addition to COAs, end points may be measured by a biomarker or survival. The end-point hierarchy (the ordering of primary and secondary end points for analysis) depends on the time horizon of the disease and the identification of what is useful and relevant to define treatment benefit in the clinical trial COU; that is, it must capture the important benefits (defined as either improved efficacy or reduced risk compared with other treatment, placebo, or best supportive care). Thus, the COA measurement strategy should focus not only on patients' reports of meaningful treatment benefits but also on the expected treatment effects, and be positioned in the end-point hierarchy on the basis of the clinical importance of the outcome to support a conclusion of treatment benefit [41].

#### Suggested Solutions

- i. Using the understanding gained from column 1, work with clinical experts early in the design of the clinical trial program to define treatment benefit. Make sure that the relationship of

all primary and secondary end points to COA measures is as completely defined and explained as possible.

- ii. Work with a group of patients and/or caregivers while designing the clinical study to understand the meaning and importance of all potential clinical end points, especially regarding the relationship of end points to patient symptoms and caregiver observations.

**3. Challenge: Developing COA Measurement Strategy Appropriate for Nontraditional Clinical Trial Designs.** Because many RD drugs are fast-tracked through the regulatory approval process because of the severity of the indication and the lack of available treatment options, there is increased interest in alternative approaches to studying drugs with RD indications. This includes consideration of nontraditional clinical development programs for faster, more efficient data collection (e.g., adaptive trials and N of 1 trials), and the utilization of alternative study designs, end points, and statistical analyses [42].

If a COA is relevant and appropriate, the RD COA strategy must be feasible within the context of the study design—alternative or traditional—that is chosen for demonstration of treatment benefit and risk keeping in mind that the COA may be the primary end point of the study.

#### Suggested Solutions

- i. Focus on measurement strategies that emphasize short-term outcomes for the trial and then collect longer-term outcomes in postapproval observational studies or in patient registries.
- ii. Coordinate with product development leads early in the program to understand the COU, for example, targeted timelines and clinical trial design, study sites. Ensure that the instrument will support the time frame for end-point data collection.
- iii. Symptoms that will not improve within the clinical trial time period, even if important to patients, will not be useful to measure if the treatment is intended to improve symptoms. Symptoms that occur rarely, or those that may change slowly, may not show change if assessed weekly, or, depending on the length of the study, may not change within the expected time frame for study completion. Understand the baseline status of patients to be enrolled in the clinical trial; improvement in symptoms cannot be measured if the population to be enrolled has no symptoms at baseline but the incidence of new symptoms, and their impact on patient functioning and HRQoL, may be important to measure.
- iv. Interact with the regulatory agencies early in product development to get their advice on treatment benefit strategies based on their experience with other RD programs.

**4. Challenge: RD Clinical Trials are Likely to Be Multinational and Include Patients in Multiple Age Ranges.** Because of small patient populations, RD clinical trials are typically multinational and often include individuals across a broader range of demographic characteristics, for example, age groups. The progressive nature of many RDs can be expected to cause substantial variation in treatment effect, as well as effect size, across patients in different stages of disease, as well as across patients with varying disease progression during the course of the study.

#### Suggested Solutions

- i. Where possible, plan to stratify patients by one or two relevant characteristics (nationality, age group, disease severity at baseline, disease subtypes, if known) to understand systematic differences in outcomes, and enable standardization of measurement of treatment benefit understanding that this will have an impact on the COA needed.

- ii. Rely on clinical expertise experienced with treating patients with the disease of interest to provide additional information on disease manifestations.
- iii. Carefully consider cultural relevance of outcomes and undertake appropriate translation and cultural adaptation in line with previous ISPOR guidances [43].
  - i. Evaluate the cultural equivalence of the instruments to be included in the study across all relevant regional populations.
- iv. Use technology such as ePRO or other to provide more standardization to the COA reporting experience.
- v. Consider a measurement strategy that includes multiple types of measures (PROs, ClinROs, and ObsROs) to capture outcomes data for both children and adults, or for patients with varying degrees of disability. In this case, the measurement and analysis strategy will need to be carefully considered because PROs and ObsROs, for example, represent different perspectives, are not comparable measures, and therefore cannot be used interchangeably or combined to make up an end-point evaluation. In a case in which patients may be too young or may experience a decline throughout the course of the clinical trial and cannot report for themselves at all times, an ObsRO might be prioritized whereas any patient reports captured can be supportive.

**5. Challenge: RD Presentation Can Change Over the Trajectory of the Illness.** Signs, symptoms, and feelings may not be stable over the course of the trial or across different age groups. Disease manifestations can vary across the lifespan, and changing developmental characteristics (e.g., verbal ability) can influence patients' experience of their illness as well as their abilities to self-report. Patients with progressive disease may worsen over time and be unable to complete self-report instruments at later points in the study, or those with more progressed or severe disease may be unable to self-report whereas those with less severe involvement may be capable of completing a PRO.

Over time children may become able to independently complete a PRO measure in the study, whereas at the start of the study they were unable to do so. The symptoms associated with an RD can change as well. For example, eosinophilic esophagitis is a chronic disease with signs and symptoms that differ by age. In infants, food refusal is commonly observed. School-age children often suffer from gastro-esophageal reflux-like symptoms, vomiting, and abdominal pain. Adolescents and adults experience mostly dysphagia with solids and food impaction [44,45]. In addition, the activities that are important to children may change as they age. Relevance of specific items addressing the impacts of the condition must be established for all included age groups and different items or activities that measure the same underlying construct may need to be included in the instrument.

#### Suggested Solutions

- i. In longitudinal studies, or in studies that include a wide range of patient age groups or disease severities, it may be necessary to administer measures in different formats. Using parallel forms of instruments measuring the same constructs may be required; for example, the Canadian Haemophilia Outcomes—Kids Life Assessment Tool (CHO-KLAT) was developed to measure symptoms in pediatric patients with severe hemophilia A [46]. Several different forms were developed for use in different age groups, including an instrument specifically aimed at younger children, another for adolescents, and an ObsRO version for completion by parents of very young children. (for a case study example, see Appendix 3 in Supplemental Materials found at <http://dx.doi.org/10.1016/j.jval.2017.05.015>).
- a. Focus on measures of symptom relief (e.g., reductions in severity, duration, or frequency) if treatment benefit does not include slowing or preventing progression of disease [20].

**Table 4 – Challenges and suggested solutions: Selecting an existing clinical outcome assessment or items that measure the COI in the appropriate COU.**

Challenges	Consider using item banks	Select subscales or items relevant to the COI from existing instruments	Increase instrument validation study sample by including patients with related conditions	Consider including an existing generic COA instrument	Consider using a multiattribute questionnaire or questionnaire battery that can be customized to individual patient's symptom profile	Use electronic data capture methods
Few/no disease-specific COAs available	✓	✓	✓	✓	✓	✓
Heterogeneity of RD population	✓					✓

COA, clinical outcome assessment; COI, concept of interest; COU, context of use; RD, rare disease.

- b. Where possible, focus on core symptoms that are characteristic of the RD across age groups and over time, and that are expected to be affected by the treatment Mechanism of Action (MOA). Although some symptoms may be age-specific, a core set that appears to be most common across the trajectory should be kept consistent even where the condition changes over time.
- ii. Focus on measures of activities of daily living or social functioning for patients who will remain severely disabled, even with treatment [20]. However, be aware that in studies that include patients with a range of disease severities, stages of progression, or developmental stages, the measure content must be reflective of the range of patient abilities to avoid floor and ceiling effects.
- iii. Behavioral manifestations of the same symptom may vary by age group. Conduct interviews with clinicians with expertise in the specific RD, caretakers, and/or patients to understand how to measure such symptoms over time or in study participants of different ages; adapt COAs for these variations.

- iv. As above, consider the end point and analysis strategy carefully. In some cases, different versions of PROs that have similar content or domains could be combined to represent a single end point, whereas measures with different reporters are likely not appropriate to combine to make up a single end point.

*Column 3: Challenges and solutions: Selecting/developing outcome measures*

Once the COI and COU have been established, the process of selecting, adapting, and validating the COA measure(s) for a specific application can begin. Few disease-specific COA instruments with published evidence of measurement properties are available for use in most RDs. Thus, when embarking on evaluating whether there is an existing COA instrument that is suitable for use in a specific patient population, special attention needs to be given to establishing the most precise definition of the COI and the COU as possible to ensure that the selected instruments are fit for purpose.

**Table 5 – Methodological challenges in developing or adapting an instrument—Qualitative studies.**

Challenges	Identify main themes based on various sources	Use only very broad codes to represent general domains	Conduct CE studies using not just patients but also anyone who has an intimate knowledge of the patient	Focus on saturation at the symptom level rather than the impact level	Consider conducting a hybrid CE/cognitive interview study	Consider alternative strategies to achieve cross-cultural equivalence	Examine cultural context and norms as part of establishing content validity within each country where the COA is expected to be used
Concept saturation	✓	✓	✓	✓			
CE and cognitive interviews			✓		✓		✓
Cultural and linguistic equivalence						✓	✓

CE, concept elicitation; COA, clinical outcome assessment.

**Table 6 – Methodological challenges in developing or adapting an instrument—Quantitative studies.**

Challenges	Use nonparametric statistics	Use continuous variables where possible	Conduct sensitivity analysis to provide more information about the variability of results	Assess psychometric properties using phase 2 data	Consider increasing the sample size by including patients who have similar RDs to the one of interest	Consider conducting test-retest reliability studies while patients are onsite with second assessment at home	Consider using electronic or telephonic data collection methods	Consider constructing standardized clinical scenarios	Use qualitative studies of patients and experts to support meaningful change estimates	Use any clinical data available on individual patient change on the COA	Evaluate results from clinical trials conducted in similar populations	Use exit interviews with clinical trial participants to establish definition of meaningful change
Evaluating psychometric properties	✓	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓
Test-retest reliability						✓						
Interrater reliability							✓					
Sensitivity to change, responder definition			✓						✓	✓	✓	✓

COA, clinical outcome assessments; RD, rare disease.

As previously stated, because of the size and nature of RD patient populations, the standard methods of adapting or developing COAs may not be feasible. These methods must be modified to allow for the successful development of valid and reliable measures used to construct end points in planned RD clinical trials. This is especially true when conducting studies to document the instrument’s content validity (both qualitative and quantitative) and to evaluate the measurement properties (reliability, construct validity, ability to detect change) of the instrument.

In addition, we recommend taking into account from the beginning that most applications in RD involve multinational clinical trials because patients with these diseases are located across the globe. Where the selected instrument has not been translated into relevant languages using industry-standard methods, translation and cross-cultural adaptation is advisable as discussed in ISPOR translation and cultural adaptation Good Research Practice Task Force Reports [47,48]. Translatability assessment is an alternative when full adaptation is not possible [49]. Adhering to these good practices in cross-cultural research is important to achieve equivalence of content and permit pooling of data. RD studies may involve small samples from multiple countries and languages, and thus conceptual and measurement equivalence is important in using COAs to assess treatment benefit.

Selected challenges and types of potential solutions when selecting or developing a COA in RDs are listed in Tables 4 to 6.

**1. Challenge: Selecting an Existing COA or Items that Measure the COI in the Appropriate COU.** Use existing item banks and COA instruments on the target population or similar populations where possible. Selecting existing items or full instruments to measure the COI is a practical solution given the obstacles associated with the development of a *de novo* COA for use in RD populations (e.g., small sample sizes, lack of understanding of the disease natural history, and frequently limited time and resources to engage in a full COA development program).

Although some existing COA instruments can be used without modifications, the evaluation process will typically indicate that modifications of existing items or instruments are necessary to enhance their relevance to the target population and their ability to detect treatment differences. When evaluating whether existing COA items and instruments can be selected and/or modified for use in a specific clinical development program, following the methods outlined in the ISPOR task force report on the use of existing PRO instruments and their modification [50] is recommended. Table 4 summarizes the challenges and potential solutions for identifying an appropriate existing instrument to adapt to the COU when no condition-specific COA is available.

**2. Challenge: Few or No Condition-Specific Outcomes Instruments Are Available.**

**Suggested Solutions**

- i. Consider using item banks previously created such as Patient-Reported Outcomes Measurement Information System banks or banks created by the investigator from relevant instruments. Select appropriate items that match the COI and the COU. Ensure that the items adequately cover the concerns in the RD population of interest by interviewing clinical experts who are familiar with this population. Regardless of whether the items have been cognitively tested in other populations, the items and the instrument generated will need to be tested for the specific clinical trial population and proposed COU.
- ii. Select instruments closest to the COI that can be disaggregated, if possible, to include only those subscales or items relevant to the COI. Again, additional validation may be

- needed, as per Rothman et al. [50], particularly if the instrument is modified for the specific COI and COU.
- iii. If there are other RDs with clinical characteristics similar to those evaluated in the clinical trial, consider whether it is clinically valid to increase the instrument validation study sample size by including patients with these related conditions. For example, symptoms of Gaucher disease are similar to those observed in patients with Pompe disease and Niemann-Pick disease. Similarly, if a disease-specific instrument exists for a closely related RD, consider using or adapting it for the population of interest. Note that the selected instrument must have demonstrated validity for this COU, and it is important to make sure that this strategy is acceptable to regulators before embarking upon this approach.
  - iv. If appropriate and feasible, consider qualitative interviews in patients with the condition of interest who are ineligible or do not wish to participate in the clinical trial for reasons unrelated to clinical characteristics. However, when choosing an instrument developed for a patient population different from the clinical trial population, be aware that there is risk of using a potentially uninterpretable measure without the full assessment of its adequacy in the new population. Small cognitive debriefing studies and pilot tests with even one or two patients may be helpful in determining the measure's fitness for purpose in such situations.
  - v. If no RD-specific COAs are available, consider including an existing generic COA instrument, if appropriate to the COI and examined for content validity, that is, relevance and comprehensiveness of the items, with the population experiencing the RD. Generic measures may not address the most specific concerns of the patient population and may be less sensitive to condition-specific changes. However, if appropriate, as judged by the patients themselves and with data confirming measurement properties, generic measures can provide a "standardized assessment" and comparative data that can be taken into account by regulatory and coverage/payment bodies [51,52]. This strategy can also allow for comparisons across age groups, ethnicities, and cultural or regional groups, and may aid in the interpretation of results by permitting comparisons with the general population. Well-developed generic instruments are also more likely to include culturally adapted translations. Because they are familiar to some regulators, generic instruments may increase the probability of regulatory acceptance (especially in non-US markets). Generic measures must be used with caution because the potentially small signal size and statistical significance observed when nonspecific assessment instruments are used in RD populations may not be sufficient to build a compelling story to satisfy regulatory needs.
  - vi. Where a COA with appropriate content is available but has not been longitudinally tested in the intended COU, consider including the COA as an exploratory end point and use the clinical trial to explore both the measurement properties including ability to detect change and interpretation of that change observed for the instrument under development and begin to understand the relationships between the COA and other end points included to measure treatment benefit.

**3. Challenge: Heterogeneity Impacting Measurement Ability Across Disease Spectrum.** When there is substantial heterogeneity in RD symptoms within the patient population, discrete outcomes measurable across the entire spectrum of disease may not be possible [53].

#### Suggested Solutions

- i. Consider using a multiattribute questionnaire or a questionnaire battery that can be customized to the individual

patient's symptom profile using skip patterns or computer adaptive testing. Individualized measures, known as patient-generated outcomes or individualized questionnaires, are instruments that attempt to capture the aspects of disease and functioning that are most important or most bothersome to an individual patient. They do not consist of predefined domains or weights, but elicit them from each individual subject. These patient-specific domains and weights are then used to derive an overall score [54] and are attractive in studying RD populations, although insufficient evidence has accumulated to support the use of such patient-generated instruments in clinical trials. The use of item banks or computer adaptive tests to elicit more individually tailored responses may be more feasible. Although it may be difficult to develop RD-specific measures using modern test theory methods given the large sample size requirements for calibration if not already calibrated in existing banks, previously developed measures based on these methods should be considered carefully. Item banks are being extended in Patient-Reported Outcomes Measurement Information System to include more specific items and this approach may prove more feasible for RD trials [55].

- ii. Electronic data collection is especially useful in such situations because it can minimize potential problems due to inappropriate or missed responses that pose a risk in paper-based instruments with skip patterns. Navigating study participants only to the items relevant to them can reduce respondent burden. Beginning COA development in an electronic format also can streamline the cognitive interviewing process because experience with the device can be captured from the beginning of COA development rather than after migrating the paper-based measure content to the electronic environment.

**Table 5** summarizes the challenges and potential solutions in conducting qualitative research to support the content validity of a measure for use in a RD patient population.

**4. Challenge: Developing or Adapting an Instrument—Concept Saturation.** Saturation of relevant concepts may be difficult to achieve given the small size of the qualitative study sample where CE occurs. This is especially difficult when there is heterogeneity in the RD population, when there is great regional variability in patient experience, or when patients in various disease progression states are included in the study. Also, for some RDs, patients may have difficulty distinguishing RD-related symptoms from those associated with iatrogenic or comorbid conditions. These factors make reaching saturation and establishing content validity difficult to achieve with patient input alone.

#### Suggested Solutions

- i. Identify main themes based on various sources including not just CE interviews but case reports, other published literature, or clinical-expert opinion. Document consensus on the most salient and important concepts across multiple sources of information including the literature, interviews with clinical experts or caregivers, as well as patient interviews.
- ii. Use only very broad codes to represent general concepts and domains.
- iii. Conduct CE studies using not just patients but also caregivers, clinicians, even other family members or teachers—anyone who has an intimate knowledge of the patient. Similarly, it may be helpful to gather general population input for understandability of the draft item content using samples that are similar to the target RD population with respect to cognitive ability, nationality or ethnicity. Typically, these methods are

not recommended, but may be a necessary concession in very small RD populations.

- iv. Revise the conceptual framework of the measure and focus on saturation at the symptom level rather than the impact level due to the heterogeneity in demographic characteristics, clinical manifestations, and caregiver and social support.
- v. A CE study with fewer than 10 patients, instead of the more typical 30 to 50 patients, is another option because this may be sufficient to reach saturation [56]. To minimize bias or the possibility that important concepts are missed, investigators should try to ensure that, despite the small sample size, patients representing the variability in the relevant disease characteristics (symptoms, severity, etc.) are included in the sample.

**5. Challenge: Developing or Adapting an Instrument – Difficulties Adapting an Instrument—Qualitative Studies.** When developing and validating COA instruments, strict methodology would require two separate patient populations, one for CE and one for cognitive interviewing. In the RD field, the patient population typically may not be large enough to conduct two different analyses.

#### Suggested Solutions

- i. Consider conducting a hybrid CE/cognitive interview study to document content validity for a novel patient population (before implementing study, work with regulators to ensure there is acceptance of this approach). Such studies combine a brief CE interview first in which major disease-relevant concepts are elicited, followed by a standard cognitive interview of the draft COA questionnaire, which has been identified, adapted, or developed before the qualitative study using literature review and expert input.

This allows for emergent concepts to be mapped to existing questionnaire concepts to determine whether all questionnaire concepts are relevant and ensure that none are missing. The cognitive portion of the interview evaluates the appropriateness of the concepts, domains, and items included in the instrument as well as patients' ability to understand the instrument instructions, items, and response options, and can complete the instrument accurately and without difficulty. This solution may allow for a condensed time frame for evaluation of content validity in addition to obviating the need for multiple interviews with separate patient populations. It is recommended that interviews be conducted in waves to allow for adjustments to be made to the instrument as needed; these waves do not typically need to include a large number of respondents; 3–5 per wave may be adequate depending on the extent of revisions and the size of the available sample population. A translatability assessment can provide evidence of cultural equivalence needed.

**6. Challenge: Developing or Adapting an Instrument—Cross-Cultural and Linguistic Comparability.** Given the small size of most RD populations, most clinical trials are conducted in a multinational, multilingual sample to achieve required sample sizes for evaluation of treatment efficacy. This requires a number of special methodological considerations for instrument development/adaptation and validation.

#### Suggested Solutions

- i. Because the standard translation and linguistic validation methods required may not be feasible in small RD populations, alternative strategies to achieve cross-cultural equivalence in such situations should be considered. For example,

it may be possible to carry out a single forward translation by a bilingual clinical expert in each target country, followed by a multidisciplinary expert committee review that compares backtranslated versions.

- ii. Cultural context and norms should be examined as part of establishing content validity within each country where the COA is expected to be used if feasible. This may be done through translatability assessment given the variety of cultures in RD studies and the challenge of conducting translations in each region. The appropriateness and relevance of a COA instrument for a specific region or culture can be examined during the translatability assessment. Translatability is the evaluation of the extent to which a COA measure can be meaningfully translated into another language. A “meaningful translation” in the context of international clinical trials is one that is conceptually equivalent to the source text and culturally and linguistically appropriate in the target country to confirm the validity of comparisons across different groups and pooling of data.
- iii. If possible, conducting cognitive interviews with a small number of patients, caregivers, or clinicians within the regions or cultures of interest will provide evidence of the relevance of the measure to different RD populations.

**7. Challenge: Developing or Adapting an Instrument—Evaluating Measurement Properties.** Table 6 summarizes the challenges and potential solutions for establishing the quantitative properties of COAs for use in RD clinical trials.

Standard statistical tests for evaluating psychometric properties of measures may be underpowered because of the small sample size as well as the subtypes of the condition. Furthermore, the geographic dispersion of patients with RD as well as the heterogeneity of the population may pose challenges to psychometric evaluation. For example, the heterogeneity of many RDs can confound the association between age and functional status if patient subgroups have not been completely defined. Stable disease criteria can be difficult to identify in some RDs because of the lack of a well-defined natural history and an incomplete understanding of rate of progression of the condition, making intrarater reliability and longitudinal psychometric analyses challenging.

#### Suggested Solutions

- i. For small sample sizes, it may be advisable to use nonparametric statistics in evaluating measurement properties. Given the sometimes skewed distributions of items in a COA instrument in RD, using nonparametric statistics is necessary. These statistics will include the typical parameters of mean and variance but, unlike parametric statistics, nonparametric statistics make no assumptions about the probability distributions of the variables being assessed [57].
- ii. Maximize chances of achieving statistically significant findings where possible by using continuous variables.
- iii. Conduct sensitivity analysis to provide more information about the variability of results in different patient groups or clinical scenarios.
- iv. If possible, match or stratify on important prognostic factors to increase precision of the estimates.
- v. If the COA instrument was included in a phase 2 clinical trial, it may be possible to assess psychometric properties using data collected in this study rather than conducting a separate pilot study of the instrument. This should be discussed with regulatory authorities before implementing the study to ensure acceptance of instrument validation results.

- vi. When a separate psychometric validation study is needed, consider increasing the sample size by including patients who have other RDs similar to the one of interest or whose clinical characteristics are similar to those to be evaluated in the clinical trial (if known).
- vii. For longitudinal psychometric analysis, use results from evaluations recommended in Column 2, Challenges 1 to construct criteria for stable (as possible) disease. These criteria should be confirmed with clinical experts.
- viii. Another potential strategy for conducting longitudinal psychometric analysis for RD COA instruments is to collect event data at the time of COA measurement (date of latest acute event, frequency and severity of acute events, etc.) to obtain a better understanding of any changes in health status that may impact results.

**8. Challenge: Developing or Adapting an Instrument—Test-Retest Reliability.** Estimating appropriate time intervals between tests may be difficult due to external factors such as a long duration between study visits to distant clinics or variations across different regions in availability of treatments for acute symptom exacerbations.

#### Suggested Solutions

- i. Recruit patients for instrument validation studies through major treatment centers (e.g., locations patients travel to for their routine care). When patients travel to central locations for their treatment, consider conducting test-retest reliability studies while they are onsite. Alternatively, evaluate the measure once during a clinic visit and follow up with a second assessment in the patient's home (this may necessitate mixing modes of data collection).
- ii. Consider using electronic or telephonic data collection methods (e.g., computer-assisted telephone interviews, where sample size is sufficient) that allow respondents to complete instruments offsite. Keep in mind that it will be necessary to confirm that patients are clinically stable to ensure that retest results are valid.

**9. Challenge: Developing or Adapting an Instrument—Interrater Reliability for ClinROs, ObsROs, or PerfOs.** Dispersion of patients over a wide geographic area can make it difficult to obtain simultaneous observations of more than one caregiver, nonclinical observer, or clinician. Moreover, if cross-national populations are included, differences in clinical protocols for diagnosis and treatment and/or cultural differences in the interpretation of symptoms may result in between-country variations.

#### Suggested Solutions

- i. Consider constructing standardized clinical scenarios (e.g., written descriptions, pictures, and online video clips) for observers to use to complete the COA remotely; then, evaluate agreement on the basis of their instrument responses to these scenarios.
- ii. Use results from evaluations of patient/caregiver/clinician perceptions to inform interpretation of any regional or demographic differences.
- iii. If patient numbers allow, stratify inter- or intrarater reliability (IRR) analysis by country or region and report within-group IRR as well as total IRR results.

**10. Challenge: Developing or Adapting an Instrument—Longitudinal Analysis to Evaluate Ability to Detect Change and Determine Change for Establishing Responder Criteria.** The small

sample sizes and geographic dispersion of patients with RD make longitudinal assessment both outside and inside global clinical trials difficult. Sponsors will need end points that can detect small changes that are meaningful to patients, clinicians, and payers across all regions and cultures. Sample sizes may be insufficient to obtain meaningful data for estimation of responder definition, or there may be different responder definitions for different regions.

#### Suggested Solutions

- i. Use patients and experts to support estimates of meaningful changes with qualitative interviews or small studies.
- ii. Use any clinical data available on individual patient change on the COA to inform an estimate of likely changes in a clinical trial setting.
- iii. Evaluate results from clinical trials conducted in similar populations to estimate change and the responder criteria for examination.
- iv. Use exit interviews with clinical trial participants in control and treatment groups to establish their assessment of meaningfulness of change experienced in the trial.

#### Conclusions

There is a growing recognition of the importance of the patient voice in understanding treatment benefit to improve clinical and medical care coverage decisions. Patients and their caregivers are demanding that these factors be taken into account. In the past, obtaining the patient perspective was rarely attempted in RD clinical trials [53]. Although perhaps not the sole reason, certainly the lack of valid measures and the difficulties in developing or adapting measures for this purpose are major contributors to this gap in our understanding of RD treatment efficacy.

This ISPOR Emerging Good Practices for Outcomes Research Task Force Report is an initial attempt to delineate the obstacles encountered when measuring clinical outcomes in patients with RD, and to provide some potential solutions to these challenges. These emerging good practices can serve as a starting point for the development of an inventory of sound, pragmatic, and creative solutions that can lead to an increase in the number of RD clinical trials with COA end points and improve our understanding of treatment benefits from the patients' perspective. Follow-on work will be needed to learn how best to interpret results given the lack of understanding of natural disease history for many RDs, as well as the small and often heterogeneous patient populations.

Other challenges to be addressed as experience increases will include working with regulatory agencies to achieve a clear set of standards that are practical for evaluating the validity of RD COA end points and additional work to arrive at feasible statistical tests to demonstrate measure reliability and psychometric properties in very small populations.

This report does not address considerations relating to clinical trial design for RD treatments, nor the suitability of RD COA measures to inform cost-effectiveness studies, value frameworks, health technology assessments, and/or payer decisions. However, although the payer perspective on the types and uses of COA information for supporting access and reimbursement decisions is not addressed in this article, it is important to understand given the cost and organizational budget impact of many new RD treatments, and the growth in number of treatment options for patients with RD.

In summary, the explosion of new treatments for rare disorders is a great opportunity for researchers, clinicians, and, of

course, patients to finally have some viable options that can extend life and decrease suffering. However, the options can be bewildering to choose from without good evidence as to their actual benefit to the patient. It is crucial during medical product development to incorporate the patient perspective to provide the RD community with valid, useful information to aid patients, caregivers, and clinicians in treatment decision making. Despite the many conceptual and methodological challenges that remain to be solved, COAs are an important component of clinical trials and medical product development moving forward. Addressing these obstacles will be both exciting and necessary for improved patient outcomes.

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## Supplemental materials

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