



Patient-Reported Outcomes in Orphan Drug Clinical Trials

INNOVATIVE APPROACHES TO IMPROVING STUDY DATA

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On February 28, 2018, the 11th international Rare Disease Day was celebrated around the world. Co-founded in 2008 by the European Organisation for Rare Diseases (EURORDIS) and joined in 2009 by National Organization for Rare Diseases (NORD) in the US and rare disease advocates in other countries, this day is designed to increase awareness of the effect of rare diseases on patients and their families, including hardships endured to seek accurate diagnoses and appropriate treatments, as well as the need to support the development of orphan drugs and provide access to such drugs.

The key to development of orphan drugs is the optimization of data in pre-approval assessments of the compounds under review, including effective tools to identify patient-reported outcomes. These measures are particularly impactful due to the limited and heterogeneous patient populations associated with rare diseases. Innovative psychometric approaches are currently being developed and utilized to address these specific requirements, and to improve the quality and depth of these studies.

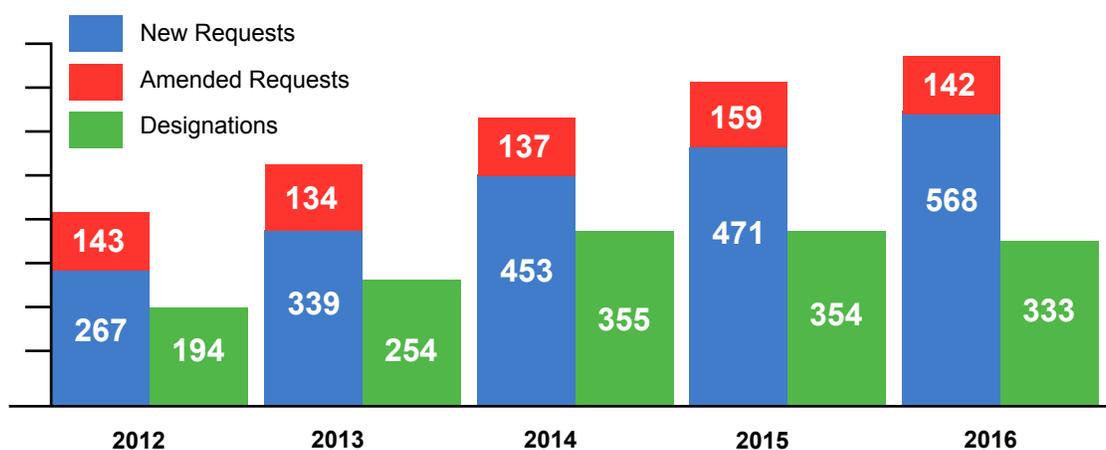
This white paper presents:

- the background and identification of the challenges inherent in orphan drug analyses
- an overview and discussion of the innovative psychometric approaches being used in developing patient-reported outcome (PRO) and clinical outcome assessment (COA) measures

Background and Challenges

In 1983 the US passed the Orphan Drug Act (ODA) to provide financial incentives to life sciences companies to conduct clinical research into diagnostics and treatments for rare diseases, defined as those affecting fewer than 200,000 persons in the US.¹ Prior to the ODA, only 10 drugs for rare disease were approved by the Food and Drug Administration (FDA).² As Table 1 shows, while the number of requests for orphan-drug-status has increased, the number of designations has remained relatively stable since 2014. Although the orphan designation has its benefits for drug and device sponsors, marketing applications are still subject to the FDA's standard regulatory requirements and process, including adequate and well-controlled trials.^{3,4} According to the FDA's regulatory standard 21CFR Part 314.126, adequate and well-controlled studies are those in which "the methods of assessment of subjects' response are well-defined and reliable. The protocol for the study and the report of results should explain the variables measured, the methods of observation, and criteria used to assess response."³

Table 1: Orphan Drug Designations by Year



Source: <https://www.fda.gov/downloads/ForIndustry/DevelopingProductsforRareDiseasesConditions/HowtoapplyforOrphanProductDesignation/UCM565068.pdf>

Interestingly, although the passage of the ODA was heavily influenced by NORD, signifying a growing recognition of the importance of the patient voice in policy decisions, the use of PROs as endpoints in rare disease trials has not been given its due. Regardless of the increase in the number of drugs receiving orphan status and gaining registration approval, the number of pharmaceuticals for rare diseases with PROs in the label remains small.⁵ The FDA defines PRO measures as "any report of the status of a patient's health condition that comes directly from the patient without interpretation of the patient's response by a clinician or anyone else."⁶ Patient or caregiver reports of symptoms, ability to function, and satisfaction with treatment are as critical for rare diseases, if not more so, than for common diseases. Indeed, with increased sensitivity for including the patient-voice in drug development, patients and caregivers are the experts on their experiences with a condition and its treatment. PROs and observer-reported outcomes (ObsROs) require the voice of the patient/caregiver to make sure the concepts measured are important, relevant, and meaningful to them (i.e. have content validity).⁷ To hone these patient/caregiver reports into measurable concepts, the expertise of questionnaire developers and psychometricians is needed to ensure that the PROs are valid, reliable, and interpretable.⁸

FDA Guidance

In 2009, the FDA published its "Final Guidance to Industry" and, in 2015, the "Rare Diseases: Common Issues in Drug Development Guidance to Industry." Neither of the documents provided specific guidance for how to address PRO instrument development and validation issues in rare diseases where sample size may be limited.⁹ The FDA's Roadmap to Patient Focused Outcome Measurement in Clinical Trials¹⁰ mandates that sponsors must understand

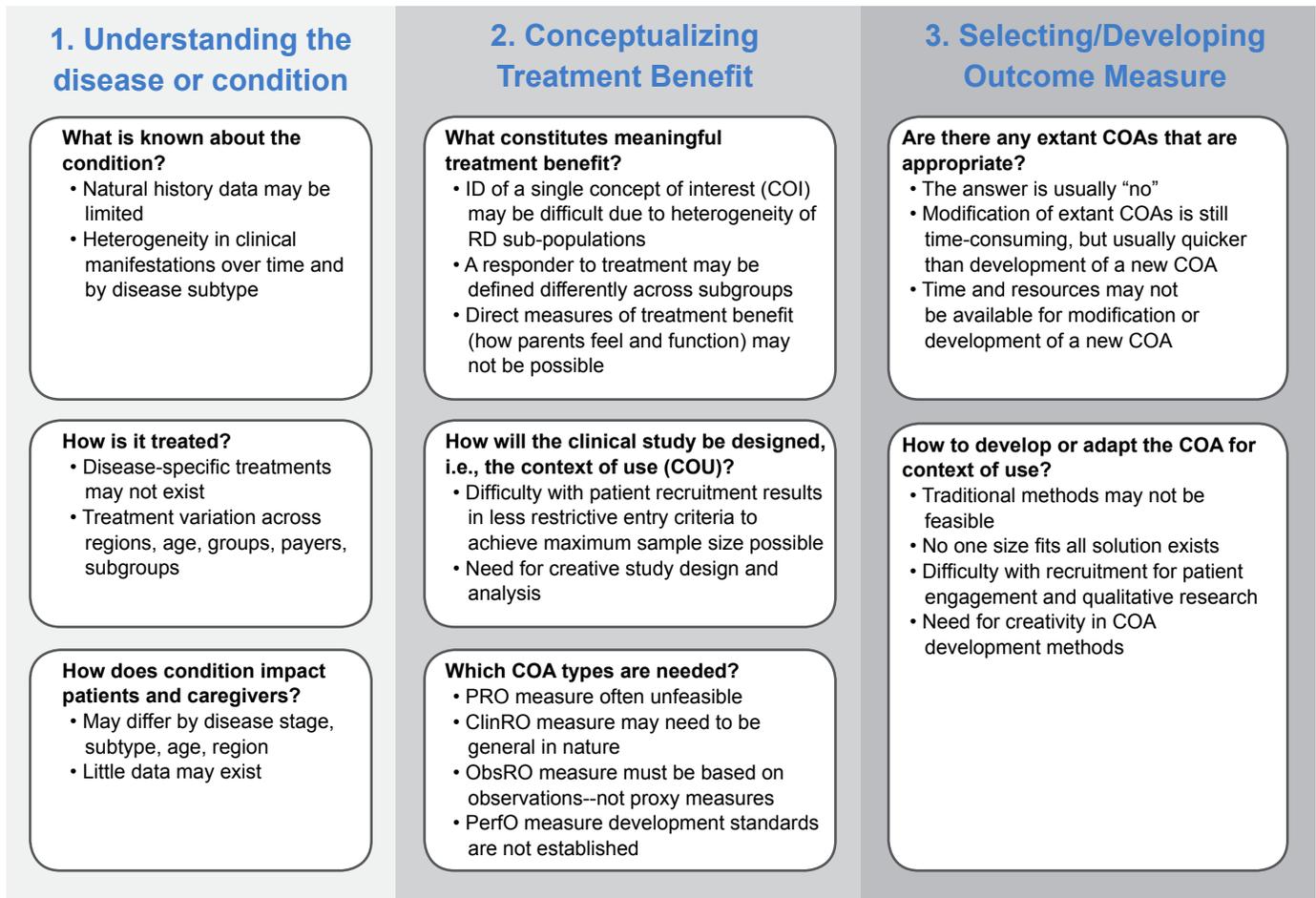
the disease or condition, conceptualize the treatment benefits, and select/develop COAs including ObsROs, PROs, clinician reports (ClinROs), and performance measures (PerfOs). The Roadmap is followed for COA development for the more common diseases, but adhering to it in a rare disease developmental program poses complex issues in clinical trials regarding:

- the selection of endpoints and the use of surrogate endpoints for accelerated approval
- clinical meaningfulness of primary and key secondary endpoints
- a tolerable benefit/risk profile and what safety endpoints to use
- the assessment of dose selection
- the selection, development, and trial analysis of PROs

The challenges in COA development in rare diseases relative to more common diseases in using the Roadmap was highlighted by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force for COA Measurement in Rare Diseases Clinical Trials which overlaid the challenges on the Roadmap (See Figure 2).¹¹ Indeed, the critique has been raised that applying the PRO/COA roadmap to development and selection of rare disease outcomes may be like putting a square peg in a round hole and constrain “exploration of potentially novel methodological approaches” and “refined to exclude issues related to trial design, or COA date-related economic or value assessments”.¹²

The FDA’s Roadmap to Patient Focused Outcome Measurement in Clinical Trials¹⁰ mandates that sponsors must understand the disease or condition.

Figure 2. Challenges for Implementing COA Endpoints in Rare Disease Clinical Trials*



Source: <https://www.ncbi.nlm.nih.gov/pubmed/28712612> *Adapted from Patient-Reported Outcome and Observer-Reported Outcome Assessment in Rare Disease Clinical Trials: An ISPOR COA Emerging Good Practices Task Force Report

On December 13, 2016, the 21st Century Cures Medical Innovation Bill was passed, again reinforcing the need for patient input into drug development. As part of the FDA's willingness and desire to include patient/caregiver input into medical product development and regulatory decision making, the FDA conducted 24 disease-specific patient-focused drug development (PFDD) meetings to better understand patient and caregiver perspectives on conditions and their treatments between the years 2013 and 2017. Approximately half of these meetings were devoted to a rare disease. These meetings have led to the "Patient-Focused Drug Development: Guidance I – Collecting Comprehensive and Representative Input" workshop held on December 18, 2017.

Innovative Approaches to PRO Development for Rare Diseases – Case Studies

In response to the FDA Guidelines and the ISPOR Taskforce report, innovative psychometric approaches are currently being developed and used to address the specific PRO requirements of orphan drug trials and to improve the quality and depth of their data. The goal of any PRO development project is to understand the measurement properties of the set of items comprising a would-be instrument, insuring that the approaches deal with the issues of small sample size and patient heterogeneity in rare diseases, key obstacles in developing valid and reliable PROs for orphan drugs.

At the International Society for Quality of Life Research (ISOQOL) in 2017, Wirth and Houts¹³ gave a presentation on the development of PROs using longitudinal Item Response Theory (IRT) approaches with a sample size of n=25. The authors note that "Capitalizing on repeated measurements, it is possible to estimate psychometric characteristics for an assessment even when sample size is small. While there are limitations and caveats to consider when using these models, longitudinal IRT modeling may be especially beneficial when developing measures for rare conditions and diseases in difficult-to-reach populations."

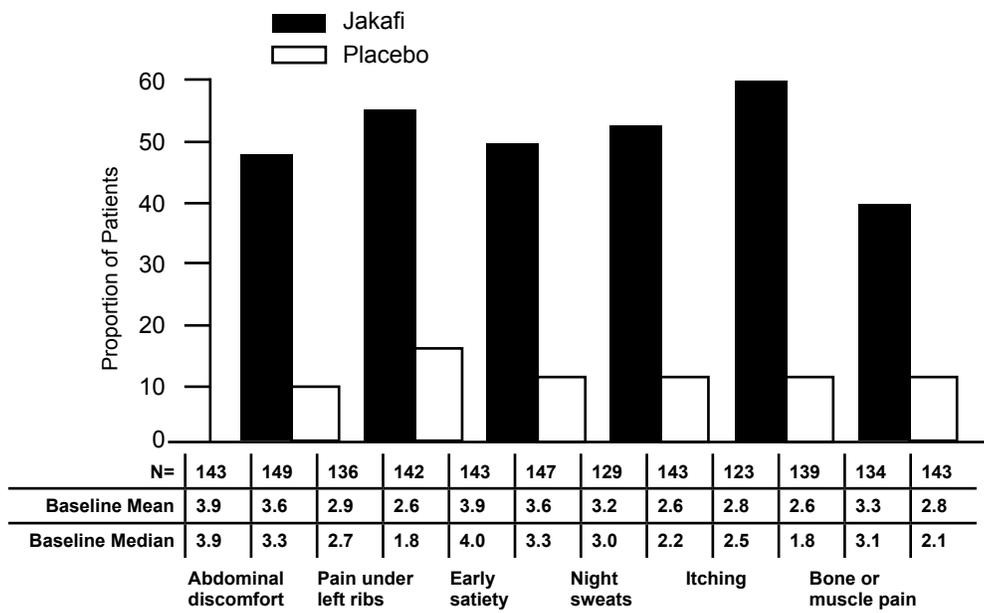
There have been specific cases in which treatments have received a PRO claim on their label and it is instructive to examine what factors contributed to their label approval. In general, these cases provided solutions to the various issues raised with their development and use in orphan drugs, including:

- Providing the needed evidence for content validity, reliability, construct validity, and responsiveness
- Considering a target study population where the detection of the drug effect is more likely, or elevated risk patients, those who are likely to have the events of interest
- Choosing patients who are more likely to respond to treatment
- Selecting endpoints important to patients and most likely to reflect benefit in HRQoL
- Evaluating responder definitions for key impairments via anchor and distribution-based methods to determine validity

Case I: Modified an already validated instrument early in product development

2011 NDA 202192: Jakafi (ruxolitinib phosphate) was approved as a new molecular entity in 2011 for intermediate or high-risk myelofibrosis - including for primary myelofibrosis, post-polycythemia vera myelofibrosis and post-essential thrombocythemia myelofibrosis. It was given priority review and orphan product designation after 1 double-blind, randomized, placebo-controlled trial and 1 open-label trial. The Jakafi case is well known as it was the first oncology drug to receive a PRO in the label since the publication of the draft Guidance to Industry in 2006. Approval was obtained after demonstrating a reduction in splenomegaly (reduction in spleen volume of 35% at 24 weeks [RCT] or 48 weeks [Open label])¹⁴ and an increase in the proportion of patients with a 50% or greater reduction on the modified Myelofibrosis Symptom Assessment Score PRO (MF-SAS) Diary V2. The Jakafi story is a perfect exemplar of following the Guidance to Industry regarding qualitative and quantitative research with the target population to provide the needed evidence for content validity, reliability, construct validity, and responsiveness, as well as early engagement and multiple interactions with the FDA.¹⁵ In addition, the results were unequivocal for ruxolitinib vs. placebo as illustrated in Figure 3 below.

Figure 3. Proportions of Patients With Myelofibrosis Achieving 50% or Greater Reduction in Individual Symptom Scores at Week 24



KEY MESSAGE

This study exemplifies the ability to obtain a PRO label claim including measures of reliability, validity, and the ability to detect change, as well as robust PRO findings in clinical trials of rare diseases.

Source: http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/202192s009lbl.pdf accessed on 021818

Case II: Included an “enriched sample”, used modified validated PRO and symptoms measure important to patients

NDA 206038: Cystic fibrosis (CF) Orkambi (lumacaftor/ivacaftor combination oral tablet) was approved in 2015 for the treatment of patients age 12 years and older who are homozygous for F508del mutation in the CFTR gene. This drug, considered a new molecular entity, was granted orphan drug status and priority review. Its approval was based on the evidence from two randomized, double-blind, placebo-controlled, 24-week clinical trials in 1108 clinically stable patients with CF. The PRO in the label measured the absolute change from baseline to Week 24 in the Cystic Fibrosis Questionnaire Revised (CFQ-R) Respiratory Domain score - a measure of respiratory symptoms relevant to patients with CF (i.e., cough, sputum production, difficulty breathing).¹⁶ The solutions in the trials and in the qualitative work to provide supportive evidence for content validity of the CFQ-R included:

- Selecting the study population where the detection of the drug effect is more likely
- Choosing elevated risk patients, those who are likely to have the events of interest
- Choosing patients who are more likely to respond to treatment (e.g., have a specific biomarker, some genetic marker, some reason to believe that a given patient will respond to the treatment)

KEY MESSAGE

“The cystic fibrosis drug Kalydeco (ivacaftor) is an example of this successful strategy. The drug works only in the 4 percent of CF patients with a specific genetic abnormality. If the drug had been studied on the entire CF population, it would have been impossible to detect the drug’s effect.”

Robert Temple, M.D., US Food and Drug Administration

Source: FDA Voice <https://blogs.fda.gov/fdavoices/index.php/2012/12/strategies-for-more-successful-drug-trials/>

Conclusion

The critical need for the development of orphan drugs has been clearly identified and supported for over 35 years. Essential to these development efforts is the optimization of data in pre-approval assessments of the compounds under review, including effective tools to identify patient-reported outcomes. Challenges remain, particularly in adapting measures developed for large scale clinical study patient populations to the smaller-sized groups associated with rare diseases. However, considerable progress has already been made, using innovative qualitative and psychometric approaches, to provide PRO tools designed for the orphan drug development process, and to improve the quality and depth of these clinical studies. Further refinement is essential, particularly in the standardization and integration of PRO measures for rare diseases into the COA process.

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