The Benefits of Early Engagement with Patient-Reported Outcomes Strategies in Clinical Product Development

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KEY POINTS . . .

Patient-reported outcome (PRO) data collection is often considered only late in the clinical product development process, producing data that may be suboptimal for the demonstration of treatment benefits.

Considering PROs from the beginning of product development can overcome these issues, providing PRO evidence of treatment benefits that meets regulatory standards.

Early PRO strategies could be further capitalized on to generate evidence to inform trial design, product development, and marketing decisions.

The use of patient-reported outcomes (PROs) to assess the value of health care products and interventions in clinical trials is becoming more commonplace [1]. This should come as no real surprise; some product or intervention benefits are not easily measured using clinical tools, particularly in treatment areas such as pain and mental health. Even in treatment areas where clinical indicators can be measured, PROs can demonstrate additional benefits such as increased work productivity, providing particularly valuable evidence for products or interventions that aim to improve functioning and alleviate symptoms rather than to cure. What is more, PRO data can be used to quantify the trade-offs that patients are willing to accept, which can aid regulatory agencies in weighing the benefits and risks associated with a particular intervention or product [2]. Early engagement with PRO strategies can improve the quality and usefulness of the PRO data collected in clinical trials, and could be further used to generate information about a product's benefits or patient preferences to provide valuable insight to inform decision making.

What are PROs?

A PRO is a measure of any aspect of patient health that is directly elicited from the patient themselves, rather than based on laboratory tests or clinical opinions [3]. Generic PRO instruments include scales that measure health-related quality of life (HRQoL), such as the SF-36 [4], while disease-specific PRO instruments are tailored to provide information about the specific disease-related symptoms experienced by a patient, such as the FACT-B [5] (Functional Assessment of Cancer Therapy – Breast) for breast cancer. For generic PROs, there is a further sub-category of preference-based PRO instruments such as the EQ-5D [6]. These are linked to an algorithm which applies weights to the different outcomes based on population preferences for that health state, thereby valuing health states on the basis of whether their impact is desirable or not, and producing a health utility value that quantifies the severity of a health state in a single value that is common across all disease areas.

How are PROs currently used in clinical product development?

PRO data are currently used for two main reasons in clinical product development. Firstly, and perhaps most commonly, PRO data are used in labelling claims or product summaries to outline treatment benefits beyond those captured using clinical markers. For curative or life-extending treatments, PROs are usually a secondary or exploratory endpoint, providing supporting evidence for treatment benefits, although the intervention will be judged predominantly on whether it is physiologically effective. In contrast, for treatments that aim to alleviate symptoms rather than to cure, PRO evidence may constitute a primary efficacy endpoint. For all interventions, improvements in functioning or HRQoL measured using PRO instruments can demonstrate differences between products and their comparators, providing additional information to regulatory agencies, payers and consumers [7].

Secondly, preference-based PRO data is collected in clinical trials to calculate utilities of different health states for input into cost-utility analyses (CUAs) of new products. These CUAs form one of the cornerstones of health-technology appraisals (HTAs) in the UK [8], and are given prominence in HTA guidelines around the world [9]; therefore, appropriate utility measures are essential for accurate economic modelling, and ultimately regulatory and reimbursement approval.

In response to the increasing use of PRO data in recent years, regulatory agencies such as the US Food and Drug Administration (FDA) and professional bodies such as the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) have released documentation to try to strengthen the quality of the PRO data on which health decisions are based. This includes the FDA guidance for industry regarding PRO instruments used for labelling claims [3], as well as multiple papers published by an ISPOR Task Force providing recommendations for a variety of specific situations, including ensuring content validity in existing [10] and new PRO >

instruments [11], validating electronic PRO instruments [12], and assessment of PROs in children and adolescents [13].

The problems with current PRO strategies

Investigation of clinical trials registries has demonstrated that PRO data are most often collected at the phase III trial stage [1]. Late engagement can result in the collection of inadequate PRO data, which in turn can create problems in the demonstration of treatment value, both in terms of disease-specific product benefits and for economic evaluation. Moreover, belated consideration of PRO strategies prevents the industry from taking opportunities to exploit a source of information that could inform future trial design, product development decisions, and marketing strategies.

Poor planning can limit the quality and usefulness of the PRO data collected, particularly where PROs have been included as a secondary or exploratory endpoint rather than the primary outcome. While companies may be quite specific about the treatment benefits that they aim to measure, they may be uncertain about which PRO instruments are most suitable, and fast decisions may result in suboptimal choices. Indeed, a recent review found that although 44.8% FDA submissions between 2006 and 2010 reported PRO data collection as a pivotal element within their clinical trials, only 24.1% were granted PRO label claims [14]. Of these PRO label claim denials, 38% were primarily due to the instrument being unfit for purpose, with a further 27% of rejections cited as resulting from problematic study design, data quality, or interpretation of the results, all of which are likely to arise from insufficient planning.

In order to facilitate appropriate use of PRO instruments in clinical trials, the FDA generated guidelines [3] that specify the criteria to which PRO instrument development or modification should adhere. These guidelines are comprehensive, emphasizing the need to provide evidence to demonstrate that the PRO instrument accurately measures the concepts it claims to measure (content validity), measures these reliably over different time points and across different individuals (reliability), and uses scales that are sensitive to the detection of change in symptoms. In particular, there are considerations around the suitability of the instrument for the population being assessed, optimal frequency of assessment to minimize patient burden, while ensuring symptom change is accurately captured and appropriateness of the recall period to ensure accuracy.

In situations where a suitable instrument does not yet exist, it may be necessary to modify an existing PRO instrument in order to measure treatment benefits effectively, or to develop a new PRO instrument from scratch. FDA recommendations [3] for best practice in the modification or development of PROs outline a lengthy, iterative process that should include patient input, data collection, and statistical assessment of validity and reliability (Figure). Recommendations from other organizations such as ISPOR emphasize the same points, highlighting the importance of patient involvement in instrument development, and the necessity for analyses to confirm validity, reliability, and sensitivity to change.

Economic models are often considered later still in the development pathway, following the collection of phase III data, at which point it is sometimes evident that opportunities to collect utilities data were missed completely. Without early consideration of the health states and populations for which utilities data is required, it is common that even where utilities have been collected, the data across clinical trials for a particular product are fragmented and do not represent the health states needed for economic models, impeding robust CUA.

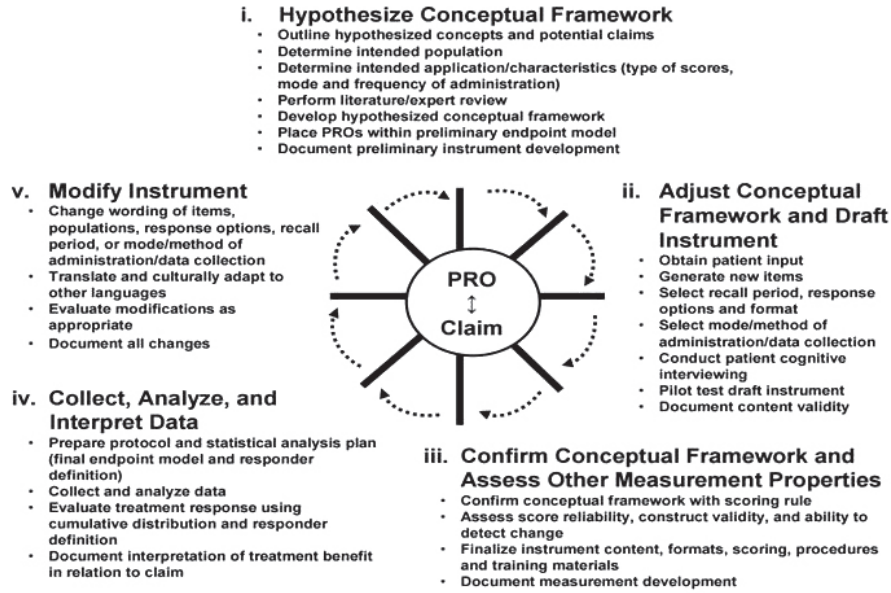
The benefits of early engagement

Overcoming current problems

Consideration of PRO strategies early in the product development pathway could reduce problems regarding the quality and coverage of PRO data. Developing PRO strategies prior to phase III trials would provide the time to conduct a thorough review of the available PRO instruments, allowing for the selection of the most suitable PRO measure. In situations where no validated PRO exists that meets trial requirements, early consideration of these requirements would provide companies with the time to develop or modify a suitable instrument in line with regulatory guidelines.

To optimize the collection of PRO data for health economic modelling, strategies combining early consideration of PRO data collection with early health economic modelling should be implemented. Early models explore the uncertainty within the cost-effectiveness context of the product, identifying any data gaps and which parameters drive the cost effectiveness of the product, as well as target populations for whom the product may be most effective or cost effective. Early models are

Figure 1: Graphic outlining the recommended PRO instrument development process, 'Development of a PRO Instrument: An Iterative Process' taken from FDA guidelines [3].



also an important source of information for key investment decisions with regard to early pricing strategies, phase III trial design, and the positioning of the product within the competitive market. At a minimum, manufacturers should consider CUAs when designing utilities data collection. An ISPOR Task Force has also suggested that manufacturers may consider designing supplementary studies of cross-sections of the anticipated licensed population outside of the tight exclusions for clinical trials in order to generate accurate utility values [15].

Unexploited benefits of early engagement

Moreover, early PRO data can be further capitalized on to inform trial design, product development, and marketing decisions. For example, PRO data collection in early trials can identify key treatment benefits that can be explored in greater detail in later trials, or identify subgroups for whom treatment benefits are greater, allowing the product development and marketing strategies to position themselves appropriately from an early stage. Even where it is not appropriate or possible to collect PRO data prior to phase III trials, early consideration of strategy may provide guidance for the design of the phase III and IV trials regarding the frequency of, and intervals between, assessments and the optimum trial length for demonstration of treatment benefits.

PRO strategies for clinical product development need not be restricted to consider only 'outcomes' in the strict sense of the word, rather they can be expanded to incorporate collection of patient preferences. For example, using discrete-choice experiments to identify how far patients value one treatment benefit over another, or whether they are willing to accept a greater risk of particular adverse events in order to benefit from treatment-related health gains. Although the collection of data for marketing purposes typically does not occur until the phase IV trial stage [16], early collection of PRO and preference data could identify the target market and most appealing product features early on to provide advantages in market positioning and product development strategies. There is no reason why PRO data could not be used in the pre-development stage even, where analysis of patient experiences and preferences can reveal the aspects of care they consider most important. This information could be used in advance of product development to guide the design of the product so that its key features target the aspects most likely to improve the health and well-being of the patient population.

Conclusion

Given the arguments in favor, we propose that manufacturers should develop clear and flexible PRO strategies from the beginning of the product development program, or even in in the pre-development phase. These should consider firstly, the ways in which the PRO data may be used (i.e., as an efficacy endpoint, to calculate health state utilities, to inform trial design). These objectives will be essential to assessing the optimal schedule for any necessary supporting research (e.g., review of suitable PRO instruments, development of a new PRO instrument), as well as for the PRO data collection itself in order to achieve those aims. It is important that any strategy maintains flexibility and is developed with contingency plans so that subsequent steps dependent on the results of earlier steps can be adopted efficiently. High-quality PRO data, especially when combined with equally early economic evaluation, can support label claims, cost-effectiveness claims, and provide evidence that will be useful for marketing. Early engagement with PRO strategies provides an opportunity to gain early insight into the factors that drive regulatory and reimbursement decisions at the time of launch.

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References

[1] Scoggins JF, Patrick DL. The use of patient-reported outcomes instruments in registered clinical trials: Evidence from ClinicalTrials.gov. Contemp Clin Trials 2009;30:289-92. [2] Gonzalez JM, Craig BM, Muhlbacher AC. Choice Defines Value: Using Discrete-Choice Experiments to Understand and Inform Health Care Decisions. 2013. [3] FDA. Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims Food and Drug Administration; 2009. [4] Ware JE, Snow KK, Kolinski M, Gandeck B. SF-36 Health survey manual and interpretation guide.: The Health Institute, New England Medical Centre, Boston, MA; 1993. [5] Brady MJ, Cella DF, Mo F, et al. Reliability and validity of the Functional Assessment of Cancer Therapy-Breast quality-of-life instrument. J Clin Oncol 1997;15:974-86. [6] Rabin R, Oemar M, Oppe M, et al. EQ-5D-5L user guide. Basic information on how to use the EQ-5D-5L instrument. Rotterdam: EuroQol Group 2011. [7] Doward LC, Gnanasakthy A, Baker MG. Patient reported outcomes: looking beyond the label claim. Health Qual Life Out 2010;8. [8] NICE. Guide to the methods of technology appraisal 2013 (PMG9). 2013. [9] Jakubiak-Lasocka J, Jakubczyk M. Cost-effectiveness versus Cost-Utility Analyses: What Are the Motives Behind Using Each and How Do Their Results Differ?—A Polish Example. Value Health Regional 2014;4:66-74. [10] Rothman M, Burke L, Erickson P, et al. Use of Existing Patient-Reported Outcome (PRO) Instruments and Their Modification: The ISPOR Good Research Practices for Evaluating and Documenting Content Validity for the Use of Existing Instruments and Their Modification PRO Task Force Report. Value Health 2009;12:1075-83. [11] Patrick DL, Burke LB, Gwaltney CJ, et al. Content Validity-Establishing and Reporting the Evidence in Newly Developed Patient-Reported Outcomes (PRO) Instruments for Medical Product Evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 2-Assessing Respondent Understanding. Value Health 2011;14:978-88. [12] Zbrozek A, Hebert J, Gogates G, et al. Validation of Electronic Systems to Collect Patient-Reported Outcome (PRO) Data-Recommendations for Clinical Trial Teams: Report of the ISPOR ePRO Systems Validation Good Research Practices Task Force. Value Health 2013;16:480-89. [13] Matza L, Alexander JJ, Bullinger M, et al. Pediatric patient-reported outcome instruments for research to support medical product labeling: Report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health 2013;16:461-79. [14] DeMuro C, Clark M, Mordin M, et al. Reasons for Rejection of Patient-Reported Outcome Label Claims: A Compilation Based on a Review of Patient-Reported Outcome Use among New Molecular Entities and Biologic License Applications, 2006-2010. Value Health 2012;15:443-48. [15] Wolowacz S, Briggs AH, Belozeroff V, et al. Estimating Health-State Utility for Economic Models in Clinical Studies: An ISPOR Good Research Practices Task Force Report. Value Health 2016;19:704-19. [16] In: Lo B, Field MJ, editors. Conflict of Interest in Medical Research, Education, and Practice. Washington (DC); 2009. ■

Additional information:

For additional information on clinical product development, see the Report of the ISPOR Clinical Outcome Assessment Emerging Good Practices Task Force summary on page 23.

For further information on ISPOR Patient Centered Special Interest group, go to https://www.ispor.org/sigs/PatientCentered.aspx