Patient-reported outcomes: How useful are they?

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Abstract
Patient-reported outcomes (PROs) are any report on the status of a patient's health condition as told by the patient him or herself or through an interview, without any interpretation by a clinician or anyone else. They generate information on those aspects of health, disease, and treatment that are only known to the patient suffering from the condition, and include any assessment of symptoms, functional status, psychological and social well-being, health related quality of life, adherence, persistence, satisfaction, or preferences for healthcare interventions from the perspective of the individual. In clinical research, PROs are endpoints of observational studies and provide data on patients in real life situations. The appropriate selection of PRO and of PRO instruments as well as the accurate interpretation and reporting of PRO results are essential to the reliability of evidence generated. PRO assessment has become a vital component in the design of patient registries, which should serve to improve the provision of healthcare, to inform decision makers, and to gain knowledge on the true effects of treatments on patients in the long term.

Introduction
Patient-reported outcomes (PROs) reflect what patients think and how they feel about their disease and treatment(s) they receive.[1] They provide information on patients' views, attitudes, and behaviours that ultimately determine the effectiveness of therapies in real life situations and usual clinical practice. PROs are captured and measured by specifically designed and validated instruments and methods to cover many aspects of the individual such as social and psychological well-being, physical and social functioning, health related quality of life (HRQoL), preferences, adherence, persistence, and satisfaction. Because they depict the results of treatments in real life they are most frequently measured in observational studies.[2] As a result, PROs complement highly valuable data on the efficacy and safety information usually generated in clinical trials. This article gives definitions of PRO, descriptions of tools used, and reporting requirements as well as the fundamentals for arguing that PRO assessment in observational studies are generators of data that are as important as data from clinical trials.

What are patient-reported outcomes?
PRO is defined 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" by the US Food and Drug Administration (FDA).[3] In Europe, the European Medicines Agency (EMA)[4] adds that PROs are "based on patient's perception of a disease and its treatment(s)" and that PRO is "an umbrella term covering both single dimension and multi-dimension measures of symptoms, HRQoL, health status, adherence to treatment, and satisfaction with treatment".[4]

PROs provide information on those aspects of health, disease, and treatment that are only known to the patient suffering from the condition, such as the frequency, severity, and emotional repercussion of symptoms, the impact of the illness in everyday life, or the factors determining beliefs and behaviours towards treatments.[5]. They allow investigators and clinicians to know about their patients' thoughts and perceptions on the healthcare process and

Table 1. Type of PRO instruments and related information

Type of PRO instrument	Concept measured	Advantages	Disadvantages	Example
Generic	Health status and outcomes of illness	Applicable to the general population and to a wide range of patient groups	Some levels of detail that may be relevant to specific disease groups are sacrificed	36-Item Short Form Survey Instrument (SF-36)
		Assess an extensive variety of aspects of health and disease	Not sensitive to changes in health that may be clinically important	
		Suitable for use across a broad range of health problems		
		Suitable for comparing treatments for different disease groups		
		Useful for assessing the impact of healthcare technologies in which therapeutic effects are still uncertain		
Utility measures	Preferences or values attached to individual health states	Produces information on the overall value of health states to society	Labour-intensive and time-consuming	5-dimension-5 level EuroQol questionnaire (EQ-5D-5L)
		Useful for economic evaluation studies	Respondents may have difficulty understanding the tasks they are required to perform	
Disease specific	Patient's perceptions of a specific disease or health problem	Relevant to patients suffering from the disease	Health status scores cannot be compared with those obtained for the general population	Audit of Diabetes Dependent Quality of Life (ADDQoL)
		Relevant to clinicians as it is responsive to clinically important changes resulting from interventions directed to control the health problem	Comparisons across treatments for different diseases are not possible	
			May not be sensible for detecting side effects or unforeseen effects of treatment	
Population specific	Particular demographic groups' perceptions of disease (e.g. children or elderly people)	Content more relevant to the group in question	Health status scores cannot be compared with those obtained for the general population	Child Health and Illness Profile-Child Edition (CHIP-CE)
		Specifically tailored format (e.g. cartoon illustrations)	Comparisons across population groups may not be possible	
		More sensitive to systematic differences between population groups		
Dimension specific	Severity of symptoms (or other dimension of disease) and their impact on functioning, role activities, psychological and social well-being	Provide a more detailed assessment of a particular dimension of health	Not appropriate as a solely outcomes measure for the evaluation of the effectiveness of treatment	Brief Symptom Inventory (BSI)
Individualised	Issues, concerns, or domains of personal concern to the respondent	High content validity	Have to be administered by interview: labour-intensive and time-consuming	Schedule for the Evaluation of Individual Quality of Life (SEIQoL)

Note: Based on Oxford University Patient Report Outcomes Measurement Group[6]

Table 2. Fundamental properties of a PRO instrument

Properties	Definition
Reliability	Ability to yield the same result on serial administrations when no change in the concept being measured is expected. Individuals with the same health status or fairly the same disease situation will score similarly in the PRO instrument.
Responsiveness	Ability of the instrument to detect changes that occur over time in individuals or group of individuals who have experienced modifications on their health status or disease development (e.g. improvements, deterioration, or an unexpected event) or have received a treatment of demonstrated efficacy. The changes in the PRO instrument scores will vary accordingly in direction and magnitude as the individual's health or disease situation change in time.
Validity	Degree to which the instrument measures what it intends to measure.
Construct validity	Degree to which what was measured reflects the conceptualisation of what should be measured.
Content validity	Extent to which the instrument actually measures the concepts of interest.
Criterion validity	Extent to which the scores of the PRO measured reflect the gold standard measure of the same concept.
Minimal clinically important difference (MID)	The smallest change in score in an instrument that can be regarded as important and meaningful from the patient's or clinician's perspective.

Note: Based on Frost et al.[9]

expected results that tests, technologies, or other observers cannot unveil.[6] In this sense, accounting for PROs helps to empower patients and enhance communication among patients, healthcare providers, and decision makers. They also help to anticipate the probable effectiveness of therapies.[7]

PRO instruments

PRO instruments are the tools patients use to assess their health conditions, health status, and other physical, social, and mental functions as they perceive these. They are administered by the patient (self-reported), by a health-care provider through interviews, or by a combination of both. Responses are in the form of scoring (e.g. from 1 to 5) or ordering (e.g. highest to lowest), or by choosing amongst a set of answer options (e.g. the most and the least important), which can consist of pictures, numbers, or categories.[1] PRO instruments can be classified based on the concept they measure (Table 1 overleaf).[6]

Ideally, a PRO instrument should be specific to the concept (e.g. health status) being measured within a framework of robust evidence gathered earlier. Moreover, it should contain an optimum number of items to minimise response overload, have scales of easy use (if possible, the simplest for the intended population to understand), be reproducible, and maintain patient confidentiality.[5]

A PRO instrument can be administered on paper or electronically (e-PRO) through electronic diaries, computers, telephones, and other portable devices.[6] Compared with paper-based PROs, e-PROs are more beneficial because they

- generally reduce missing information and avoid data entry errors, which usually arise from an intermediate source,
- are immediately accessible,
- trigger alerts and notifications,
- increase patient's willingness to report sensitive information, and
- give real-time tracking of survey compliance.

However, there are some important barriers in their use such as increased expense, some cultural resistance, and limited time for patient-training.[7]

Selection of PRO instruments

Verifying that a proper PRO instrument has been selected is vital to adequately interpret results and consequently enhance the chances of publication. If PRO results are to be used in labelling claims, they should also satisfy regulatory requirements.[8] Three properties of a PRO instrument are fundamental: validity, reliability, and responsiveness (Table 2).[9] The calculation of the minimally important difference (MID) is also relevant. Beyond those critical characteristics, a series of additional aspects should also be taken into account to assess the appropriateness of the chosen PRO instrument (Table 3). If preferences for health states or for the characteristics of treatment are considered, the most appropriate method for eliciting patients' preferences should be ensured. Examples of preference assessment include ranking or rating scale, best-worst scaling, standard gamble, time trade-off, visual analogue scale, discrete choice experiment and conjoint analyses, and multi-attribute utility instruments.[10,11]

For purposes of economic evaluations, a PRO instrument should focus on less complexity, speed, and sensitivity to incremental effects on HRQoL and to choices in decision making.

However, other considerations in selecting a PRO instrument are the setting, nature, and aim of the project, and the type of healthcare decision to be made.[12] For example, a PRO instrument for registries of patients' health records should prioritise its practicality, easy administration, cost-effectiveness, low participant burden, and simple documentation with other clinical data. PRO instruments for product labelling should reinforce high validity and reliability, sensitivity to changes, instrument stability over time, and low rates of missing data. For purposes of economic evaluations, a PRO instrument should focus on less complexity, speed, and sensitivity to incremental effects on HRQoL and to choices in decision making.[13]

There are some institutions that provide accurate information on the characteristics and properties of the PRO instrument as well as use and reporting recommendations and bibliographic references. One is the Mapi Institute,

which maintains the Patient-Reported Outcome and Quality of Life Instruments Database,[14] allowing users to search a large and comprehensive database for PRO instruments. Here, the user can find the best PRO that addresses a specific research question. The On-line Guide to Quality-of-Life Assessment[15] is another database of existing HRQoL instruments. The US National Institutes of Health PROMIS Initiative[16] has developed rigorously tested item banks across a broad range of domains and subdomains that allow comparisons. The PROMIS Initiative also actively evaluates methods to achieve brevity in instruments through different techniques. Many of these measures are publicly available through the PROMIS Assessment Center.[17]

Evaluating PROs as data sets

Although PRO assessment provides very rich information at the individual level, aggregating these data to measure performance of treatments and of the healthcare system delivering care at a target population level is challenging.[9] One weakness, for example, is that results implied by patients in questionnaires or relayed by interviewers are outcomes based on patient's own assessment that may not be equivalent to particular concerns of most patients suffering the same disease.[10] Individual patients may also decide when and with whom they share their health and disease-related information, which may impede usability and access to information. Thus, these and other social issues together with economic disparities must be overcome. Current initiatives that include advanced analysis systems and predictive analytics are underway to improve data collection and statistical management of PROs at a population level.[18]

Current initiatives that include advanced analysis systems and predictive analytics are underway to improve data collection and statistical management of PROs at a population level.

In clinical research, PROs are most frequently the primary endpoint of observational studies. Their assessment have been shown to be paramount in generating information on situations where either exposing or preventing patients from receiving an intervention is unethical, but where it is conceivable to gather perspectives on the illness and to value patient preferences for other possible disease scenarios.[1] Furthermore, measuring PROs in observational studies is insightful in rare diseases. This is because reachable sample sizes are too small for conducting a clinical trial, but gathering primary data on patients' HRQoL and on the perceived determinants of disease burden are very important for healthcare decision making.[19,20]

How valuable is the assessment of PRO in healthcare?

In usual clinical practice, the differences between clinicians' and patients' understanding of the effect of disease (e.g., prevalence and severity of patients' symptoms, functional impairments, influence of disease on the individual's everyday life) and treatment have been extensively researched and reported.[17,18,19] PROs bridge these discrepancies. Furthermore, patients' direct self-reporting on health problems facilitates the discussion of important symptoms and quality-of-life aspects with healthcare professionals. This supports documentation and can help to improve disease management and positively influence clinician decisions.[1-5]

It is not surprising that a review of evaluations for approval of new pharmaceutical products by the EMA carried out between 1995 and 2003 showed more than a 30% increase in the use of HRQoLs and other PRO instruments, particularly in cancer-related treatments.[20] Similarly, about 24% of new drug approvals by the FDA between 2006 and 2010 in the US had PRO labelling.[21] This figure rose to almost 77% between 2011 and 2015 as most approvals of new

Table 3. Other aspects to be considered in the selection of a PRO instrument

Aspects	What to ask
Documentation	Is/are there formal written documentation, publications on the use of the instrument (type of research, objectives and aims, limitations, findings)?
	Is there a user manual (how to administer it, score, interpret results)
Development	How was it developed? (methods and findings for content and concept development, validation in the original and other languages, robustness of validity, responsiveness and reliability findings)
Feasibility	Are the questions, tasks and scoring easily understandable?
	Is the mode of administration or data collection too long?
Target population	Is the scale suitable for the target population (very ill people, children, elderly)?
	Is there a need for a carer to help?
Language and cultures	Are translations properly validated?
Scoring	Is there a definition of the scoring procedure and is it easy to interpret?
Interpretation	Are guidelines for interpreting scale scores and dealing with missing data available?
License for use	Is there a fee attached to the use of the PRO instrument? (copyright protection, holders, extension)
	What are the conditions for using? (considering the number of projects to be conducted with the same instrument, number of subjects in whom the instrument will be used, period of time during which the instrument will be administered; clinical practice, academic, research, private, or public entities to run or support the project)

Note: Based on Gliklich et al.[26]

products were made for diseases that traditionally rely on PROs for evaluating the benefits of treatment.[22]

PRO data collection is increasingly integrated into clinical registries to produce real world data on the effectiveness of healthcare interventions.[23] The routine measurement of PRO has become more important to inform future care planning in a feasible and efficient manner.[24] Challenges in doing so, however, include selecting the most suitable PROs and PRO instruments, overcoming logistic hurdles of PRO collection, ensuring long-term sustainability and complete data gathering, controlling for selection bias and missing information, and managing data aggregation. In order to succeed, diverse stakeholders, including payers (e.g. insurance systems), policy-makers, clinicians, patients, and researchers should cooperate to eventually find valuable and meaningful data from the PROs collected in registries. [25]

Conclusions

PROs are very useful for providing information about what patients think, how they feel, what their preferences are, and why they behave in the way they do towards their disease and treatment(s) especially in chronic, disabling, progressive, and other difficult-to-treat conditions. PROs may contain information little known to clinicians, policy makers, and regulatory authorities. These crucial data will help to determine the effectiveness and the success of treatments in usual clinical practice and real life. PROs are at the cornerstone for generating real world evidence and are a vital component of registries if these should be designed to eventually improve healthcare quality and information generation for decision making bodies. Appropriately selecting, measuring, interpreting, and reporting PRO data are fundamental.

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