Patient-Reported Outcomes in Oncology, Beyond Randomized Controlled Trials

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Abstract

The goal of the treatment of a disease has moved from treating organs and diseases through symptoms, biological parameters and imaging towards treating a human being as a whole. The treatments should deliver benefits that patients can personally perceive. However, the patient's perspective does not always match the one of those surrounding them. Illustratively, patients' symptom assessments are more predictable for daily health status, whereas clinicians' symptom measurements are more related to clinical outcomes. The term, patient-reported outcomes (PROs), includes any data that are reported directly by the patient without an intermediary, such as a family member or a healthcare professional. The use of PROs in oncology trials is increasing and the U.S. Food and Drug Administration has published guidelines on the review and evaluation of PROs. However, while PROs are increasingly used in clinical trials, they are rarely used in daily clinical practice. Further, healthcare payers are concerned with issues related to relevance, quality, and interpretability of these outcomes.

Keywords

Patient-reported outcomes (PROs) · Health-related quality of life (HRQoL) Symptom assessment · Oncology Payers · Patient preference Clinical trials

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1 Introduction

According to the World Health Organization, "Health is a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" (WHO 1946).

Over the years, the goal of treatment of a disease moved from treating organs and diseases through symptoms, biological parameters, and imaging towards treating a human being as a whole. Disease treatments should deliver benefits that patients can personally perceive as improvements in their "quality of life" and they should be able to assess as well as prevent serious events in future. For example, it only makes sense to treat hypertension if we reduce symptoms such as headaches or if we significantly reduce the risk of later occurrence of heart failure or haemorrhagic stroke. Reducing the blood pressure per se is not the ultimate objective. Because the "quality of life" can depend on factors other than health, health-related quality of life (HRQL) term was proposed for use in healthcare settings (ISPOR 2001).

2 Patient Perspective Differs from HealthCare Professional Perspective

Studies have shown that, for severe health conditions, practitioners rate the HRQL worse than patients, whereas for non-severe conditions the practitioners rate it better than the patients (Toumi 2016). However, this can be reversed when treatment-related side effects are assessed. For example, during head and neck cancer chemoradiotherapy practitioner-reported toxic effects are lower than patient self-reports (Falchook et al. 2016). Also, proxies (such as caregivers, family) can reliably report on the quality of services and on observable symptoms, but not for subjective aspects of the patient's experience, such as pain, anxiety and depression (McPherson and Addington-Hall 2003). Further, in a palliative care setting, whereas family caregivers tend to give more accurate ratings than healthcare practitioners, both proxies under-valuate the quality of life which may lead to overtreatment of symptoms (Dawber et al. 2016). This suggests that the patient's perspective does not always match the one of those surrounding them.

Further, the literature review found that patients' symptom assessments are more predictable for daily health status, whereas clinicians' symptom measurements are more related to clinical outcomes (Xiao et al. 2013). However, clinicians have the propensity to underestimate the incidence, severity or distress of symptoms experienced by cancer patients (Xiao et al. 2013). Further, a retrospective reliability analysis on cancer patients found that agreement between different clinicians when reporting adverse symptom events is moderate at best (Atkinson et al. 2012). There is also some evidence that patient-reported symptoms are more strongly correlated with clinical outcomes than practitioner-reported ones (Quinten et al. 2011).

3 Definition of PROs and Classification

The term patient-reported outcomes (PROs) includes any data that are reported directly by the patient without an intermediary, such as a family member or a healthcare professional and includes, but is not limited, to HRQL (Willke et al. 2004).

According to the US Food and Drug Administration (FDA), a PRO is "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". It can be measured in absolute terms (e.g., severity of a sign, symptom or state of a disease) or as a change from a previous measure (US Food and Drug Administration Guidance for Industry: Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labelling Claims 2009). Similarly, the European Medicines Agency's (EMA) defines a PRO as "any outcome directly evaluated by the patient and based on patient's perception of a disease and its treatment(s)" (EMA 2005).

According to EMA, PRO encompasses both single and multidimension domains such as health status and satisfaction with treatment. HRQL is a specific type of a PRO, defined as a patient's subjective perception of the effects of the disease and treatment(s) on daily life; well-being; and psychological, physical and social functioning (Patrick et al. 2011).

A PRO instrument (i.e., a questionnaire plus the information and documentation that support its use) is a means to collect data about a PRO concept (Patrick et al. 2011).

4 PROs in Oncology Clinical Trials

The use of PROs in oncology trials is increasing. Eighty-five per cent of oncology trials registered at ClinicalTrials.gov between 2006 and 2012 incorporated a PRO that evaluated HRQL or symptom measures (Zagadailov et al. 2013). Further, the use of PRO in clinical trials translates into the use of PRO in FDA labels. Twenty-four per cent of product labels approved by the FDA between 2006 and 2010 contained PRO claims, and the largest percentage of product claims was in oncology (Gnanasakthy et al. 2012).

In 2009, the FDA published a formal guidance on the review and evaluation of patient-reported outcomes (PROs) related to claims included in medical product labelling (Zagadailov et al. 2013).

In general, PRO instruments used in oncology should include four key domains (Basch 2015):

1. Physical functioning
2. Disease-related symptoms
3. Symptomatic toxicities (treatment-related adverse events)
4. Global HRQL

In practice, PRO instruments often measure HRQL or specific symptoms, such as pain, fatigue, sexual functioning or treatment-related adverse events or a combination of the domains. In both cases, the instruments can be generic or disease-specific.

Many cancer-specific instruments exist that have been developed to measure HRQL or symptoms relevant in a given cancer. Table 1 presents examples of commonly used PRO instruments in oncology (Zagadailov et al. 2013; EHA 2011).

However, the use of PRO in clinical trials should be incorporated into the clinical development plan, and care should be taken that collected data is complete. In order to be valid, PRO instruments should be carefully selected and incorporated into trial protocols and transparently analysed and reported (Brundage et al. 2013).

Table 1 Examples PRO instruments used in oncology (Zagadailov et al. 2013; EHA 2011)

Type of tool	PRO instrument
Health-related quality of life	
Generic	• SF-36 (Short Form 36-Item) • PROMIS (Patient-Reported Outcomes Measurement Information System) • EQ-5D (EuroQoL-5 Dimensions Index) • WHOQOL-100 (World Health Organization Quality of Life-100) • PROMIS (Patient-Reported Outcomes Measurement Information System) • NHP (Nottingham Health Profile) • SIP (Sickness Impact Profile)
Cancer-specific	• FLIC (Functional Living Index-Cancer) • EORTC QLQ-C30 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire) • FACT-G (Functional Assessment of Cancer Therapy-General)
Cancer-site specific	• EORTC QLQ-BR23 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Breast) • EORTC QLQ-LMC21 (European Organization for Research and Treatment of Cancer Quality of Life Questionnaire Colorectal Liver Metastases) • FACT-L (Functional Assessment of Cancer Therapy-Lung) • FACT-B (Functional Assessment of Cancer Therapy-Breast) • FACT-NCCN (Functional Assessment of Cancer Therapy—Lymphoma Symptom Index (FLymSI)—non-Hodgkin's lymphoma)
Symptoms and symptom burden	
Generic	• Visual analogue scale
Cancer-specific	• Symptom Distress Scale • Memorial Pain Assessment Card • Rotterdam Symptom Checklist • MDASI (Monroe Dunaway Anderson Symptom Assessment Inventory)
Cancer-site specific	• LCSS (Lung Cancer Symptom Scale)

5 Validity of PRO Instruments

PRO instruments are designed to capture concepts related to the health experiences of individuals. That is, how patients feel or function in relationship to their disease, condition or treatment (Patrick et al. 2011). Thus, the instruments must possess content validity that is evidence that the structure and content (items) capture the connection between the measurement concept intended by researchers and the way patients understand that concept (Patrick et al. 2011). The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Task Force on PRO Content Validity Good Research Practices lists five steps to elicit concepts for new PRO instruments and document content validity (Patrick et al. 2011):

1. Determine the context of use (medical product labelling)
2. Develop the research protocol for qualitative concept elicitation and analysis
3. Conduct the concept elicitation interviews and focus groups
4. Analyse the qualitative data
5. Document concept development and elicitation methodology and results

Content validity must be based on direct input from an adequate, diverse sample of patients from the targeted clinical study population. The final PRO instrument should be insensitive to variations in demographic and clinical characteristics and experiences within the target population (Patrick et al. 2011).

6 Other Methods to Capture Patient's Perspectives

PRO methods are not the only way to capture the patient's perspective. Patient preference methods have been described as more grounded in economic theory and are more patient-centred than the HRQL methods used in outcomes research (Bridges et al. 2007). Whereas PRO methods are concerned with measuring the patient's status along several aggregate domains, patient preference methods measure the patient's value for a specific component, or attribute, either in absolute terms or in relation to another attribute. Thus, PROs capture patient reports of outcomes in individual domains without providing information about patient preferences across domains. The relative importance of these domains is quantified by patient preference methods (Bridges et al. 2007).

Examples of patient preference methods are (Bridges et al. 2007; Ryan and Farrar 2000):

- The contingent valuation or willingness to pay (WTP)
- Discrete choice experiments (conjoint analysis)
- Exit interview (qualitative interview by a psychologist at the end of a clinical trial)

7 Value of PRO in Oncology

PFS has become the most commonly used primary end point in all lines of treatment in oncology. Clinical response and progression definitions are standardised metrics used in phase II clinical trials that describe what happens to tumours during therapy (Therasse et al. 2000). PFS is believed to translate into clinical benefit and is used as a surrogate end point of treatment efficacy in oncology clinical trials. However, such surrogate end points may not necessarily infer a patient-relevant benefit (Buyse et al. 2010; Kim and Prasad 2015; Svensson et al. 2013). Therefore, they should be underpinned by additional end points that demonstrate patient benefit which support the primary PFS end point (Friedlander et al. 2016). Symptom improvement or delay in developing symptoms may be more important from the patient's perspective than a 2-month increase in PFS (Au et al. 2010).

Extending life may only be desirable while the treatment can at least maintain the patients HRQL or ideally improve it. Therefore, clinical trials should not be restricted to just showing overall survival or PFS benefit, but should also reflect the patients HRQL. This is crucial, especially for oncology therapies that often have serious adverse events. Improvements in HRQL have been shown in treatment with certain biological therapies for lung cancer (Blackhall et al. 2014), melanoma (Long et al. 2016) and renal cancer (Cella et al. 2016).

Further, PROs have been shown to correlate with survival in patients receiving cancer therapy. Changes in HRQL scores from baseline during treatment are significant prognostic factors for survival (Ediebah et al. 2014). Also, overall quality of life (QoL) measured at the time of lung cancer diagnosis was a significant and independent prognostic factor for survival in patients with lung cancer (Sloan et al. 2012); the physical component of HRQL was associated with overall and cancer-specific survivals in patients operated on for early-stage non-small-cell lung cancer (Pompili et al. 2013); pretreatment global QoL, but not comorbidity, had significant prognostic value for survival of elderly patients with advanced non-small-cell lung cancer who were treated with chemotherapy (Maione et al. 2005).

PROs are often better predictors of survival than performance status, but studies are needed to determine whether interventions that improve PROs also increase survival and to identify explanatory mechanisms through which PROs relate to survival (Gotay et al. 2008).

However, while PROs are increasingly used in clinical trials in oncology, they are rarely used on non-trial settings. This means that oncologists cannot track patients progress or satisfaction with treatment in the clinic where PRO tools are not available. Also, clinicians may not understand the trade-offs; the patients are willing to make between improvements in objective biological outcomes such as tumour shrinkage and possible worsening in other symptoms or HRQL (Zagadailov et al. 2013). Therefore, the potential of PRO use beyond clinical trials remains underutilized.

Further, healthcare payers are concerned with issues related to relevance, quality and interpretability of PROs and may dismiss PROs that do not independently predict improved outcomes (Zagadailov et al. 2013). Quality issues can be related, for example to PRO data from open-label trials or to missing trial data (Basch et al. 2015). Also, there is no consensus among payers on the relative value of objective clinical outcomes and PROs and each may attach different valuations to each of these outcomes (Zagadailov et al. 2013).

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