

Classifying patient reported outcomes: Developments in the field suggest a new taxonomy

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In 2001 a consensus meeting of different professional bodies including the FDA recommended using the term Patient Reported Outcome to describe the type of data obtained from surveys completed by patients. Such data are more specifically defined as 'patients' report of a health condition and its treatment', a broad umbrella term that could incorporate such concepts as health-related quality of life (HRQL), satisfaction, global-health evaluation, functional status, preference, compliance, or any outcome that can be verbalized by a patient.

In 2003 an "Ad Hoc Task Force Report" emerged from the FDA Harmonisation Meeting (Acquadro et al., 2003). This report included a proposed framework for classifying PROs and was widely adopted. However the authors of this report did not anticipate the different ways in which patient-reported data now is used. In addition, they restricted their recommendations to the drug-licensing process. In 2009 a subcommittee of ISPOR's Patient Preference Methods Working Group undertook to refine the classification of patient survey data. The aims of this group were:

1. To identify how decision makers utilize patient survey data in guidance documents and published decisions.
2. To summarize methodological developments that have influenced how patient survey data are perceived and used by policy makers.
3. To propose a new taxonomy of patient survey data and methods.

1. How Decision Makers Use PRO Data

Information Sources

- FDA draft guidance on PROs
- EMEA Reflections paper (EU)
- Pharmaceutical Benefits Advisory Committee Economic sub committee guidance for manufacturers (Australia)
- National Institute for Health & Clinical Excellence guidance for manufacturers (UK)
- Tandvårds- och läkemedelsförmånsverket (Swedish reimbursement agency)
- Common Drug Review submission guidance (Canada)

Regulatory Guidance

- The FDA have published draft guidance regarding the use of PROs to support claims regarding therapeutic products with respect to licensing (FDA, 2006). Validated psychometric measures are acceptable, but preference weighted instruments such as EQ-5D are not.
- The European Medicines Regulator (EMA) take a similar view but are only willing to review HRQL data (as opposed to treatment satisfaction for example).

Reimbursement guidance

- Reimbursement bodies such as the Pharmaceutical Benefits Advisory Committee (PBAC, Australia); National Institute for Health & Clinical Excellence (NICE, UK), Common Drug Review (CDR, Canada) and Tandvårds- och läkemedelsförmånsverket (TLV, Sweden) amongst others have issued new or revised guidance in the last 2-3 years.
- These guidance documents only cover HRQL data for the estimation of quality adjusted life years (QALYs) for economic evaluation.
- While guidance documents from these reimbursement bodies vary in some technical details, fundamentally they all wish to see HRQL assessed using a generic multi-attribute utility measure which reflects the preferences of the local population derived using choice based methods such as time tradeoff or standard gamble.

Patient-Preference Data

- In 2006 FDA accepted patient data on benefit-risk tradeoff preferences in support of relicensing natalizumab for the treatment of multiple sclerosis. Similar data were evaluated for licensing the drug for the treatment of Crohn's disease in 2008. These data were captured using conjoint analysis methods (also known as discrete-choice experiments or stated-choice surveys).
- In 2007 a working group consisting of representatives from FDA, EMA, industry, and academia was established to evaluate alternative methods for quantitative benefit-risk analysis. Patient-preference data is used in several of the approaches being evaluated.
- No guidance on use of such data has been issued by regulatory authorities.

2. Proposed Taxonomy

How data are collected

Psychometric instruments

- Subjects indicate the extent to which each of a series of statements is true for them, typically using a Likert-scale response.
- Multiple statements measure the same underlying construct (such as mobility). Item responses are scored by summation or averaging, often rescaled from 0-100.
- Measurement properties are assessed statistically in terms of reliability, validity, and other metrics.
- Measures can be generic (for all disease areas), disease-specific, or intervention-specific.

Utility-weighted HRQL measures

- Subjects indicate the extent to which each of a series of statements is true for them, typically using a Likert-scale response.
- Utility weights are obtained from separate studies using time-tradeoff, standard-gamble or sometimes visual-analogue-scale methods. Weights can be elicited from general public or from patients. The cardinal utility weights reflect the value of health states.
- Responses are weighted by utilities and are combined to give a single index score measuring HRQL. The score ranges from 1.0 (full health) to 0 (dead). Some instruments allow for states worse than dead.
- Measures can be generic (for all disease areas) or disease-specific, but are restricted to measuring HRQL. Examples include the EQ-5D, Health Utilities Index and SF-6D.
- Scores are combined with outcome durations to calculate QALYs to guide decisions regarding resource allocation decisions. Measures are not usually used as a measure of efficacy or key trial endpoint.

Patient-preference measures

- Subjects evaluate tradeoffs among hypothetical treatment or intervention features. Usually used in bespoke surveys.
- Methods include choice-format conjoint analysis (also known as discrete-choice experiments or stated-choice surveys), rating-format or ranking-format conjoint analysis, and best-worst scaling (also called max-diff scaling).

- In addition to efficacy endpoints, methods used to quantify preferences for risk of adverse events, convenience and process factors.
- Results can be presented in terms of relative importance weights, likelihood someone will choose a treatment with specified features, and equivalence measures such as willingness to pay, maximum acceptable risk, and healthy-time equivalents.

How data are used

Psychometric data

- Data indicate health-related quality of life, satisfaction, symptoms, work productivity and other self-reported or proxy-reported aspects of health and wellbeing.
- Often included in clinical trials to measure endpoints that cannot be observed clinically.
- Used to measure efficacy of interventions, especially related to patient perceptions of outcomes.
- Data do not indicate the value of a state of HRQL or satisfaction.

Health-state utilities

- Data indicate the value of a health state on a single index.
- Used to provide weights for estimating QALYs in decision-analytic models.
- Support decisions regarding which products to reimburse.
- Sometimes included in clinical trials or observational studies.

Patient-preference data

- Data indicate the relative subjective importance of different health-related outcomes and health-care processes.
- May be used to support regulatory and clinical decision making, including cost-benefit analysis, generalized cost-utility analysis, and quantitative benefit-risk analysis.
- Rarely included in clinical trials.

Proposed Taxonomy

Patient viewpoints can be incorporated at several points in the evaluation process, during:

- i. the identification of outcomes
- ii. the measurement of outcomes
- iii. the valuation of outcomes
- iv. the deliberation over evidence.

- i. The identification of outcomes

A truly patient-centered approach towards the evaluation of outcomes would incorporate patients' viewpoints in the identification of the outcomes to be evaluated. In recent years there has been more attention placed on the use of qualitative methods to develop patient relevant outcomes, yet many agencies do not require such analyses. IQWiG has indicated that it considers evidence in the identification of what it has called "patient-relevant outcomes", but has yet to indicate what methods are sufficient to demonstrate relevance.

- ii. The measurement of outcomes

Patient perceptions regarding outcomes from treatment can be captured using validated survey methods. Psychometric methods have advanced considerably in recent years which gives us a much greater understanding of the measurement properties of conventional patient reported surveys. This has led the FDA and EMA to allow such measures to be reported in regulatory documents, including the label. The impact of a change in scores on such an instrument can only be interpreted with respect to changes on other measures or in terms of clinical indices. Outcomes from such instruments do not reflect values.

- iii. The valuation of outcomes

Traditionally, the QALY has been used to value health care outcomes. Patient preference methods such as WTP and conjoint analysis can also be used to value health care outcomes, but many agencies have been reluctant to accommodate such methods. IQWiG is currently exploring conjoint analysis in developing a index of patient-relevant outcomes. There is also a growing literature on using conjoint analysis to develop preference weights for PRO scales.

- iv. Deliberation

A growing number of decision making agencies include patient advocates to express the patients point of view in the deliberation process. Recent advances in the application of conjoint analysis have seen the development of a number of metrics that aid deliberation, including maximal acceptable risk.

	Identification	Measurement	Valuation	Deliberation
Qualitative	✓			
PRO		✓		
Utility/ QALY		✓	✓	
Willingness to pay	✓	✓	✓	
Conjoint analysis	✓	✓	✓	✓
Advocacy	✓			✓

Future trends

Future use of patient survey data includes:

- Routine audit of all patients treated by the UK's NHS as an index of the quality of their care.
- Burden of disease at population levels.
- Which patients should receive access to treatments (e.g. psoriasis treatments in the UK)
- Marker of treatment response in patient access schemes
- Quality audit indicator in risk-minimisation and access plans.
- New health-technology assessment strategies.
- New quantitative benefit-risk analysis methods.
- Better drug-development decision making.