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6 Patient Reported Outcomes

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Abstract

Therapeutic decisions or decisions on the uptake of new medicines should be based on evidence showing that the therapeutic intervention will lead to more benefit than harms for the patients. Under the premise that only therapies should be used that are improving the situation of patients by reducing their suffering or prolonging the life, Patient Reported Outcomes (PRO) are an important component of such evidence, which complements other health outcomes, measured through technical measurement or physician determination and reporting. In contrast to the latter, PROs are solely reflecting the effect experienced and reported by patients. This Chapter gives an overview on what the key properties of PROs are, how instruments such as questionnaires are used to collect such outcomes reports from patients, and how PROs can support clinical development as well as clinical decision making.

Measure your health by your sympathy with morning and spring
Henry David Thoreau

Contemporary healthcare systems in general strive for universal access to healthcare combined with a high level of quality and equity while, at the same time, facing the challenge of dwindling funding (economic scarcity). Increasing numbers of people (especially with an aging population that is living longer) are utilizing healthcare services and products, expecting optimal treatment leading to a high level of health and wellbeing and a greater longevity. At the same time, the number of technologies accessing the healthcare market and seeking reimbursement is proliferating. For each of the new technologies, policy makers, payers, and finally prescribers, must decide on utility and value in the context of their decision framework. As with other investment decisions, they seek to understand what they get for their money. In other words, they need to understand the cost-benefit relationship of the new technology

or technologies compared with what is already available. In addition, and at least as important as the need to understand the cost and budget impact of the new technology, the expected impact on the future health status and well-being as experienced by the patients is a driver of the decision to adopt and fund a new technology. How can we measure and assess this aspect?

The recommendation of Thoreau (to measure health by personal sympathy with morning and spring) sounds quite straight forward if not rather simple, yet the development of a commonly accepted practice is far more complex. While other Chapters in this book deal with the epidemiologic and economic aspects of the question, this Chapter will focus on the question of which kind of outcomes measures from the patient's perspective can help to complete the picture of benefits and harms of healthcare interventions.

6.1 From Physiological Measures to Patient Reported Outcome

In 1995, Wilson and Cleary conceptualized a model of patient-related outcomes by defining five types of health outcomes with increasing complexity [Wilson, 1995; Poolman, 2009]:

1. Biological and physiological variables;
2. Symptom status;
3. Functional status;
4. General health perceptions;
5. QoL.

Each type of health outcomes can be modulated by individual characteristics (individual symptom experiences, motivation, values, and preferences) and by environmental characteristics (social, economic, and psychological environment). While the symptoms are usually the reason why the patient appears in the medical practice, traditional healthcare systems focus on measuring and treating the biological and physiological components. However, patients can have abnormalities on the physiological level, such as osteoporosis or hypertension, without having symptoms, or symptoms may not always correlate with physiological diagnostic findings, as can be seen in some cases of chronic pain. Sometimes, functional status may not be fully explained by the knowledge of biological factors and symptoms, because of individual and environmental factors; let alone general health perceptions and overall QoL, which encompass much more than just a reaction to a single health defect and can only be assessed by the individual patient. Moving towards a patient-cen-

tric approach to healthcare outcomes measurement may increasingly rely on patients' reports. Functional status can be measured by using functional tests, but the findings may not be consistent with the patient's perception of his or her functional status. New technologies such as wearable electronic devices may, in the near future, also open new inroads to such measurements [Byrom, 2018]. General health perceptions, although often connected to the biological or physiological factors, become fully dependent on the individual self-assessment due to the growing impact of the individual and environmental modulators [Wilson, 1995]. Measuring outcomes through the reports of the patients can help to uncover such aspects, which are important to patients, but may not be detected by physiological measures or technical means.

Likewise, historically, decisions about adopting new technologies were mostly based on physician reported efficacy measures, which, in many cases, could be surrogate measures for the desired effect.

Today, patient-centered decisions have moved into the focus of discussion, implying that criteria used to make decisions should be relevant to patients [Holtorf, 2016]. While patients are generally less guided by surrogate outcomes such as HbA1c levels or blood pressure, they are usually more interested in questions around "length of life" or "quality of life" including factors like the degree of suffering, symptom bother, or the degree of independence and social functioning they can maintain with their disease.

In addition, recent years have seen an additional advancement: If Patient Reported Outcomes (PRO) are to inform research and decision makers on those aspects related to a disease or treatment which are important and relevant to patients, then it is necessary that patients have been involved in the development of the research instruments in order to ensure that the design is suitable to reveal these important aspects [Kirwan, 2017; Haywood, 2017a; Staniszewska, 2012; Cook, 2019].

6.2 Quality of Life, Health-Related Quality of Life, and Patient Reported Outcomes

Quality of Life

Whereas length of life or mortality are endpoints which can sooner or later be measured using a numerical scale, Quality of Life (QoL) in general is a

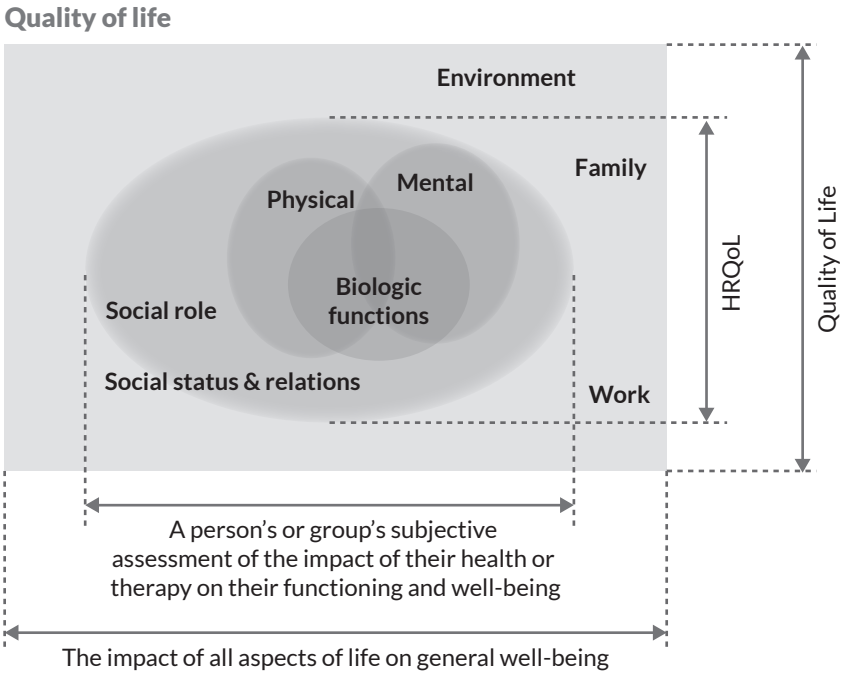

Figure 6.1. Definition of Quality of Life and Health-Related Quality of Life (adapted from [Khanna, 2007; Patrick, 2007]).

HRQoL = Health-Related Quality of Life

broad-ranging concept that describes the degree of well-being impacted by many factors such as environment, family, work, social status, or health status as depicted in Figure 6.1.

Within the field of healthcare, the interest is usually in the impact of an individual's health status on her or his quality of life, whereby "health" was already defined by the WHO in 1948 as "a state of complete physical, mental, and social well-being, and not merely the absence of disease or infirmity" [World Health Organization, 1948].

Health-Related Quality of Life

Health-Related Quality of Life (HRQoL) is a composite measure of the individual's physical health or biologic functioning, emotional or psychological state, level of independence, social relationships, and environmental forces.

Medical conditions, as well as the treatment of medical conditions, are expected to influence the HRQoL [Khanna, 2007].

When research started to examine HRQoL, data were often collected via staff-administered surveys. With increasing experience in questionnaire development and validation, direct patient self-reporting became the preferred method. The patient's perspective regarding the effectiveness of a treatment became more important than the assumed objectivity thought to be achieved through a professional interviewer. Some treatment effects are known only to the patient, e.g., localized leg pain, mild swelling, or avoidance behavior, and such aspects of disease or treatment experience might be lost if the patient's perspective was first interpreted by a health professional. In addition, some changes in clinical endpoints may not always correlate well with the patient's perception of his/her health status. For example, the 6-minute walk test used to determine the functional exercise capacity of patients with moderate-to-severe heart or lung disease may not reflect the patient's subjective ability to perform daily activities [ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories, 2002]. Consequently, the quantification of HRQoL increasingly relies on outcomes measures directly reported by the patient, i.e. "Patient Reported Outcome Measures" (PROM) [Weldring, 2013]. As formal assessments and methodologically consistent instruments, PROMs are expected to give more reliable results than informal interview-based methods [Food and Drug Administration, 2009].

Patient Reported Outcomes

A patient reported outcome was described by the Food and Drug Administration (FDA) as a type of data measuring any aspect of a patient's health status that comes directly from the patient (i.e., without the interpretation of the patient's responses by a physician or anyone else) [Patrick, 2007]. In this respect, the expressions PRO and PROM can be used interchangeably. Similarly, the European Medicines Agency (EMA) defined a PRO as "any outcome directly evaluated by the patient and based on patient's perception of a disease and its treatment(s)" [European Medicines Agency, 2005]. Hence, PRO is the general reference to the concept (outcome) of interest from the patient perspective [Patrick, 2011a].

PROs can be both single or multi-dimensional, whereas HRQoL is determined in multidimensional instruments such as questionnaires or surveys, diaries, or interviews. In addition to HRQoL, Patient Reported Outcomes

can be physiological measures, patient satisfaction, or other any experiences assessed and reported directly by the patient [Patrick, 2011a; Patrick, 2007]. Data are generated with PRO instruments, which encompass questionnaires in combination with all guidance or documentation on the questionnaire [Patrick, 2011a]. Some protagonists classify the satisfaction and experience reports into a separate category of "Patient Reported Experiences" quantified by "Patient Reported Experience Measures" (PREMs) [Weldring, 2013].

PRO questionnaires can be designed as general instruments, which can be applied across a wide range of health states, or they can be more disease-specific and symptom-oriented. Nowadays, PRO tools are used for a range of applications in clinical practice and decision making. Validated PROs determined in methodologically sound clinical studies can support endpoints, which are accepted and encouraged for substantiating drug labelling claims [Arnould, 2018; Marquis, 2011]. In the USA, the FDA issued a first guidance on PROs in 2006 (draft) and 2009 (final) to clarify the role of patient-reported data in the drug approval process and to refine standards for PRO instrument development [Trotti, 2007; Food and Drug Administration, 2006; Food and Drug Administration, 2009], which receive even more attention with a move towards "Patient Focused Drug Development" [Perfetto, 2015]. The EMA issued a Regulatory Guidance for the Use of HRQoL Measures in the Evaluation of Medicinal Products in 2005 [European Medicines Agency, 2005] and a more specific guidance on the use of PROs in the development of cancer therapies in 2016 [European Medicines Agency, 2016].

6.3 Individual Health and Circumstantial Perceptions and Experiences

However, we should not forget that people's assessment and reporting of their health or therapeutic effects are relative and can be impacted by many different factors such as age, geography, cultural background, income level, gender, family status. For instance, this can be seen in the biannual Organisation for Economic Cooperation and Development (OECD) health indicator reports [Organisation for Economic Cooperation and Development, 2017]. Figure 6.2 shows that over two-thirds of the adult respondents of the health status surveys in Belgium, Switzerland, or the USA rated their health as being good or better.

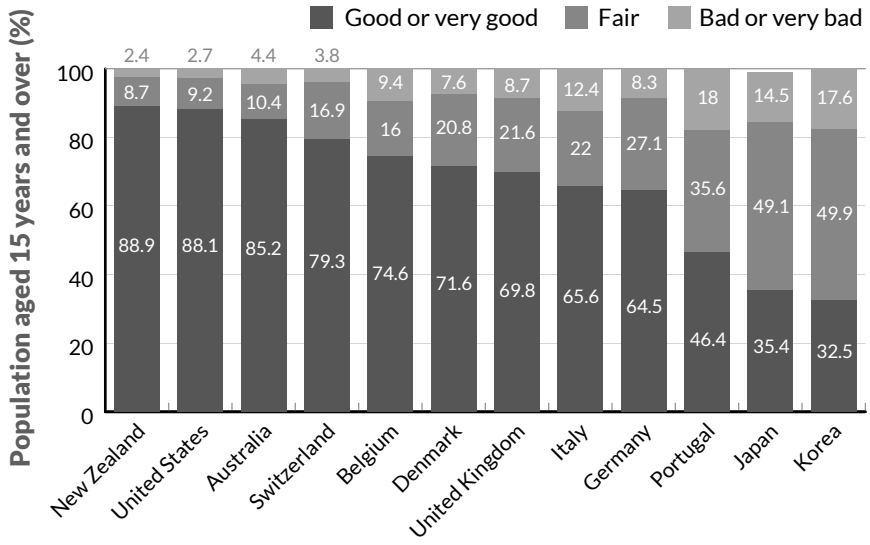

Figure 6.2. Health status reported by adults, 2015 (or nearest year). The results for New Zealand, USA, and Australia are not directly comparable with those for other countries, due to methodological differences in the survey questionnaire resulting in an upward bias. Adapted from [Organisation for Economic Cooperation and Development, 2017].

In similar surveys in Japan and Korea, just about one-third of the adult population rated their health as being good or very good. Further differences can often be observed within the countries:

- Men are more likely than women to report a better health.
- Positive rating of the own health tends to decline with age.
- People who are unemployed, retired, or inactive report poor or very poor health more often.
- Lower level of education and lower level of income usually lead to lower rating of health [Organisation for Economic Cooperation and Development, 2011].

In addition to different perceptions concerning health states, different stakeholders or different patient groups may use different vocabulary in context of the disease [Haywood, 2017a]. Therefore, it is essential to ensure validity in all the healthcare settings of interest, if a PRO-survey is used across different cultural contexts [Organisation for Economic Cooperation and Development, 2017].

6.4 Applications of PRO Instruments

PRO instruments are used for many different applications and purposes, often in chronic but also in acute diseases. PROs can:

- Help to acquire extended knowledge on **burden of diseases** to the patients or their direct or indirect social environment.
- Support **endpoint in clinical trials** [Food and Drug Administration, 2006; Food and Drug Administration, 2009; European Medicines Agency, 2005; European Medicines Agency, 2016]. To foster "Patient Focused Drug Development" [Perfetto, 2018], the FDA published in 2016 a pilot compendium on clinical outcomes assessment, which contains a list of outcomes measures and, more specifically, PRO instruments which can be used by industry in clinical trials [Food and Drug Administration, 2016]. Before using these instruments in clinical trials, their usefulness in the specific context should however be confirmed, for example through preliminary discussion with the agency. Some authors have warned that many of the listed instruments may be outdated or may not hold up against current expectations for quality and validity [Oehrlein, 2018].
- Help to **differentiate drug treatments** when there are marginal differences in drug efficacy or survival rates [Holtorf, 2018; Calvert, 2018]. In 2016, DeMuro et al. analyzed the cases where the FDA and EMA had granted label claims based on PROs and a high variability was reported in how these are used with a low degree of overlap [DeMuro, 2013]. Such differences may, to some degree, be explained by the different context and implications of a PRO-based claim in the USA and the EU, such as for the right of using such claims in direct-to-consumer advertisement [Symonds, 2014]. Especially in diseases with low patient numbers (orphan or rare diseases), the use of PROs in the development is still scattered due to the high uncertainty in the outcomes measures as well as in their usefulness for the approval or reimbursement decision process [Arnould, 2018].
- Support **patient-centered decision making in clinical practice**. The use of PROs may help patients to express better their health issues in the interaction with healthcare providers [Greenhalgh, 2018] or may help physicians in better understanding the preferences of patients in making therapeutic choices [Holtorf, 2018].
- Be used in clinical practice to monitor **outcomes in routine clinical practice** [Valderas, 2008; Lohr, 2009] or serve as quality control criteria in the routine **assessment of Health Services quality** [Weldring, 2013;

Winter, 2017; Nelson, 2015]. For example, in 2009, the UK Department of Health has issued guidance for providers and primary care commissioners on routinely measuring PROs in clinical practice under the standard NHS contract for acute services [Department of Health, 2009]. For the USA, PROs have been proposed as measures for the accountable care provider assessment [Black, 2013].

- Be used as a criterion in **Health Technology Assessment**. The use of PROs in reviews by 9 key HTA agencies across the globe (PBAC, CADTH, HAS, IQWiG, SMC, NHS Scotland, NICE, DERP, AHRQ) increased steadily, from 11.1% in 2005 to 42.5% in 2011 [Rubinstein, 2012].
- Preference-based PROs or health state utility tests can be used for the computation of the Quality-Adjusted Life-Years (QALYs) required as an element in Public Policy, **economic evaluation**, and **modeling** in the UK, Australia, Sweden, or Canada. A preference-based PRO uses an algorithm which "weights" the reported outcomes according to the preferences of the respective reference group (e.g., the general public or patient groups).
- Serve for more direct **adverse event reporting** [Banerjee, 2013]. While the patients experience the symptoms of adverse events, these are, in most of the current systems, first interpreted by the clinician and intermediate administrative personnel before they are reported in the clinical research database or the pharmacovigilance system. We may see a shift to a model in which patient-reporting is an important mechanism for monitoring subjective adverse events. Potentially, self-reporting may lead to higher quality and completeness of the collected data, while, at the same time, increasing efficiency of the reporting [Trotti, 2007]. Since July 2012, the pharmacovigilance legislation of the European Union required from all member states to set up systems for direct patient reporting of adverse events [European Medicines Agency, 2011; European Medicines Agency, 2012].
- Last not least, PROs can help **patients** to better understand the impact of their disease and of its treatment in comparison to treatment alternatives if the questionnaires have been designed to address the items of interest to patients [Holtorf, 2018]. Questions of interest may be for example, "What will happen to the pain when I take this medication? Which side effects do I have to expect? How tired will I be? Can I live longer—or longer at home—when I take this medication? What does it mean to my family, to my work, or my social network?". Therefore, patient organizations are often not only involved in the development

of the PRO questionnaires, but also use them for enriching the understanding of disease burden, understanding the patient journey, identifying/documenting areas of unmet medical need, understanding patient preferences, understanding/documenting the natural history/disease course, and identifying subgroups of patients [Cusher, 2018; Addario, 2020].

6.5 Identifying an Appropriate Instrument for Measuring PRO

The choice of instruments will have a major impact on the usefulness of PRO studies to measure psychometric outcomes or health state utilities. Selection should be guided by the purpose of the study, the "concept of interest", and the populations and pathologies for which they are designed ("context of use") [Rothman, 2007; Poolman, 2009]. In addition, there are practical issues, such as the availability in the correct language, copyrights, and access to instruments.

Health state utilities required to calculate the quality-adjusted life-years in cost-utility analyses—often as a part of health technology assessment—rate the value of a health state on a scale between 1 (full health) and 0 (death) or even negative values, which represent states assessed as worse than being dead. Preference values are usually obtained by elicitation techniques such as Standard Gamble (SG) or Time Trade-Off (TTO) from a sample of the general population or from patient populations [Brazier, 2017; Brazier, 2019]. The choice of the instruments to determine the utilities of different health states needs to be carefully planned to ensure their relevance for the use in economic models [Brazier, 2019].

How good a psychometric test or a PRO profile instrument is, is described by its **psychometric properties** with the key components "reliability" (ability to produce consistent results when repeated under the same conditions and interpreted without knowing the previous results), "validity" (the degree to which a test measures the concept it is designed to measure), and "sensitivity to change" (ability to detect change). Terwee et al. proposed a checklist of quality criteria to evaluate the methodological soundness of patient-reported outcome instruments [Terwee, 2007]. Such a set of quality criteria, as also depicted in Table 6.1, can serve as guidance in the selection of an appropriate instrument.

Content/face validity	Do the items in the instrument comprehensively test the research question?
Internal consistency	How much correlation or overlap or redundancy exists between the items of the instrument?
Criterion validity	Do the instrument's scores correlate to an existing gold standard if available?
Construct validity	Do the scores correlate with similar measures in a way that is consistent with the concept hypothesis?
Reproducibility	Will repeated measurements (test-retest) in steady populations provide similar answers?
Inter-rater reliability	Will two or more raters obtain the same results with the same instrument?
Intra-rater reliability	Will the same rater obtain the same results when using the instrument at different occasions?
Responsiveness	Will the instrument detect important changes over time?
Floor and ceiling effects	How many patients reach the highest or lowest score (preventing further detection of change over time)?
Interpretability	Can qualitative meanings be assigned to quantitative scores?

Table 6.1. Quality criteria for the selection of patient reported outcome instruments. All these criteria are co-produced with patients or patient representatives. Adapted from [Terwee, 2007; Patrick, 2011a; Patrick, 2011b; Farnik, 2012; Benjamin, 2017].

The adequacy of a PRO instrument depends on its ability to measure concepts that are relevant to patients with the medical condition, including the important positive and negative experiences of patients undergoing therapy. PRO supporting endpoints in clinical trials, like all other endpoints, must be indicators of clear and interpretable treatment benefit or harm in clinical trials [Benjamin, 2017]. There may be situations where no appropriate validated instrument is available. In this case, the development of a new dedicated instrument may be considered, but should follow a solid methodological framework. Such frameworks exist in the form of checklists and guidance documents [Patrick, 2011a; Poolman, 2009; Terwee, 2007; Farnik, 2012; Benjamin, 2017; Jackowski, 2003; Center for Drug Evaluation and Research, 2015a; Center for Drug Evaluation and Research, 2015b; Patrick, 2011b].

It should be underlined that the results can only be relevant in the context of use if the patient understands the question and choice of answers in the same way as the researcher interprets them and if they are relevant to them

[Addario, 2020]. Through co-production of PRO-instruments (see caption of Table 6.1) and by including testing steps, alignment of the research viewpoints with the patient viewpoints can be achieved [Oehrlein, 2018; Wiering, 2017; Haywood, 2017b; Cook, 2019]. Documentation of target population input as well as evaluation of patient understanding through cognitive interviewing are important activities to assure such content validity [Patrick, 2011b; Wiering, 2017].

There are a number of organizations that offer structured libraries of instruments for free or on a subscription base such as PROMIS Health Measures [U. S. Department of Health and Human Services], the COA Compendium of the FDA [Food and Drug Administration, 2016], or ePROVIDE [Mapi Trust] and PROQOLID [Pinotti, 2016].

In terms of categorization of PRO instruments, a primary distinction is between those that are generic and hence widely applicable, and those that are specific to particular diseases (e.g., asthma, hepatitis C) or concepts (e.g., fatigue) or populations (e.g., pediatric or elderly patients). Each concept can be measured by several dimensions or domains such as: emotional functioning (or disability), physical functioning, social functioning, mobility, mental functioning, or symptoms (impairments) [Fayers, 2007]. Each dimension or domain can be assessed by one or several items (questions). For the scoring, patients can than select which of several pre-defined levels (responses) best describe their situation. Many questionnaires also ask one or more general health status or QoL questions where the responses can be given on a continuous scale, which can be a graphical so-called Visual-Analogue Scale (VAS). An example of this could be "How would you rate your health on a scale between 0 = death and 100 = perfect health?").

The number of dimensions depends on the concepts to be examined by the instrument (e.g., physical mobility, cognitive functioning), and one or several questions (items) may be used to examine each dimension. For example, in the SF36, 8 domains are addressed, and in each domain, there are between 2 and 10 questions (items) asked. Depending on the question, there are 2 (yes/no) to 6 (graded from none to very much) possible answers (levels) [Stewart, 1992]. The score in each dimension is calculated from the responses to all items in this dimension. For some applications, a total score for the instrument calculated from the all dimensions may be determined [Patrick, 2007].

It is essential to consider in the development or selection of a PRO instrument the detailed measurement properties, the scoring methods, and the interpretation of the scoring.

Generic PRO tools typically assess general HRQoL or patient perceptions of healthcare across a broad range of disease or health states. Examples for such PRO instruments are the Short Form 36 (SF-36) Health Survey [Ware, 1992], the Sickness Impact Profile (SIP) [Bergner, 1981], the Nottingham Health Profile [Hunt, 1980], the Health Utilities Index [Furlong, 2001] (HUI), the EuroQol (EQ-5D) [EuroQol Group; Devlin, 2017], and the Consumer Assessment of Healthcare Providers and Systems [Squires, 2012] (CAHPS) survey instruments. While the results of "profile" instruments are usually reported as a profile across the different domains or dimensions examined, index instruments allow to extract an overall score.

Examples of disease-specific questionnaires are the Adult Asthma Quality of Life Questionnaire [Juniper, 1999] (AQLQ), the Foot and Ankle Outcome Score (FAOS) [Negahban, 2010], or the Gastro-oesophageal reflux disease Impact Scale (GIS) [Jones, 2007].

6.6 When are the Results of PROs Relevant?

As has already been mentioned above, an important pressure test for PRO instruments is the face validity and relevance of what is measured to the patients suffering from the disease and the ability to detect change. In addition, it is important to consider which change in a score, as detected by repeated use of one PRO instrument over time, is meaningful to patients. Several quantitative and qualitative techniques have been developed to estimate the degree of change or the change threshold for a specific instrument, which is meaningful for individuals or groups of patients with a specific health condition [Staunton, 2019; Wyrwich, 2013]. Likewise, several terms describe this concept of relevant change, such as "minimally important difference", "clinically important change", "minimally important change", "minimally perceptible change", or "meaningful change threshold".

What the approaches have in common is the principle that the detection of a difference below these thresholds, even if statistically significant, is to be interpreted as having no relevance for the patient and consequently, no benefit [King, 2011; Wyrwich, 2013].

Which threshold should be defined and which method should be used to do so for a PRO instrument may vary by population and context, and differing applications may require determination of different thresholds [Revicki, 2008; Coon, 2018].

6.7 Summary and Conclusion

In this Chapter, we have given a general overview of how Patient Reported Outcomes are used as one approach to achieve more patient-centric decision making in healthcare. We talked about the need to assess the value of health intervention from the perspective of the final beneficiary, the patient, because a healthcare intervention which does not make any difference to the patient may not be a good investment, even if it is less costly than other interventions.

For the practice of medicine, the notion of patient centricity has also shaped the newest revision of the "Geneva Physician's Pledge", the modern successor to the Hippocratic Oath for physicians around the world which was approved by the World Medical Association in November 2017 [World Medical Association, 2018]. The new pledge reflects the changing relationship between physicians and their patients by now giving a leading role to the patients. For the first time, the new pledge makes specific reference to respecting the "autonomy" and "dignity" of the patient and to aim for "health" and "well-being" of the patient[1].

In this review, we examined how PROs can be measured by existing and newly developed instruments and finally, we looked at different types of instruments. Short overviews like this can only scratch the surface of the wide field of Patient Reported Outcomes in modern health science, research, and health policy. However, we hope that we have been able to raise some alternative thoughts about how to measure health and health outcomes. Finally, we may see Thoreau's suggestion on how to measure health as a first hint of a two-dimensional questionnaire with two items asking "How do you like mornings?" and "How do you like spring?" as surrogates for physical, mental, and social implication of many health states. However, to give the required confidence in the usefulness of the tests' results, reliability and validity as well as its sensitivity to change, independent from external factors, would have to be established for the proposed context of use.

[1] "As a member of the medical profession: I solemnly pledge to dedicate my life to the service of humanity; the health and well-being of my patient will be my first consideration; I will respect the autonomy and dignity of my patient; …. / …" https://www.wma.net/policies-post/wma-declaration-of-geneva/

Questions

1. **Which of the following instruments measure Patient Reported Outcomes (select all that are correct)?**
   A. Blood pressure
   B. Patient satisfaction questionnaire
   C. 6-minute walking test
   D. Health-related quality of life measures
   E. Gastro-esophageal reflux disease Impact Scale
   F. Quality-adjusted life-years

2. **Why is it important to involve patients into the design and conduct of PRO research?**
   A. Patients have a different set of knowledge about the disease
   B. Patients have different skills
   C. Patients are more reliable researchers
   D. Patients can help to ensure that the survey questions are relevant to the patients

3. **For what can PROs be used?**
   A. Supporting shared decision making between doctors and patients
   B. Supporting claims of new technologies
   C. Improving the efficacy of new treatments
   D. Identifying patient needs
   E. Quality control in healthcare delivery
   F. Diagnosis of physiological status

4. **What is the advantage of generic PRO instruments?**
   A. They are cheaper
   B. Can be used in any patient population
   C. Allow comparisons across disease states
   D. Allow in depth research on disease specific aspects

5. **What is a dimension in context to the measurement of PRO?**
   A. The breadth of the patient population examined
   B. The geographic area(s) in which the study is conducted
   C. The concept of health which is tested
   D. The length of the questionnaire

6. **What is it important to determine a MCT for a PRO instrument?**
   A. This feature allows to reduce the variability of responses
   B. Without knowing the MCT, it is not possible to determine whether a change is relevant for the specific application of the instrument
   C. The MCT is an indicator on how well patients understand the question
   D. The MCT is a requirement by the European Medicines agency

Answers

1. **E, D, B (***B is sometimes categorized as Patient Reported Experience—PRE***)**
2. **A, D**
3. **A, B, D, E**
4. **B, C**
5. **C**
6. **B**

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