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KEY CONCEPTS

- 1 The evaluation of healthcare is increasingly focused on the assessment of the *outcomes* of medical interventions.
- 2 An essential patient-reported outcome is self-assessed function and well-being, or health-related quality of life (HRQOL).
- 3 In certain chronic conditions, HRQOL may be the most important health outcome to consider in assessing treatment.
- 4 Information about the impact of pharmacotherapy on HRQOL can provide additional data for making decisions regarding medication use.
- 5 HRQOL instruments can be categorized as generic/general or targeted/specific.
- 6 In HRQOL research, the quality of the data collection tool is the major determinant of the overall quality of the results.

Although it has not involved the comprehensive reform that may be necessary,¹ the medical care marketplace in the United States continues to experience change in both the financing and delivery of care.² This change is evidenced by a variety of developments, including an increase in investor-owned organizations, heightened competition, numerous mergers and acquisitions, increasingly sophisticated clinical and administrative information systems, and new financing and organizational structures. In this dynamic and increasingly competitive environment, there is a concern that healthcare quality is being compromised in the push to contain costs. 1 As a consequence, there has been a growing movement to focus the evaluation of healthcare on the assessment of the end results, or *outcomes*, associated with medical care delivery systems as well as specific medical interventions. The primary objective of this effort is to maximize the net health benefit derived from the use of finite healthcare resources.³ However, there is a serious lack of critical information as to what value is received for the tremendous amount of resources expended on medical care.⁴ This lack of critical information as to the outcomes produced is an obstacle to optimal healthcare decision making at all levels.

HEALTH OUTCOMES

Although the implicit objective of medical care is to improve health outcomes, until relatively recently, little attention was paid to the

explicit measurement of them. An outcome is one of the three components of the conceptual framework articulated by Donabedian for assessing and ensuring the quality of healthcare: *structure, process, and outcome*.⁵ For far too long, the approach to evaluating healthcare had emphasized the structure and processes involved in medical care delivery rather than the outcomes. However, healthcare regulators, payers, providers, manufacturers, and patients are placing increasing emphasis on the outcomes that medical care products and services produce.⁶ As stated by Ellwood, outcomes research is “designed to help patients, payers, and providers make rational medical care choices based on better insight into the effect of these choices on the patient’s life.”⁷

TYPES OF OUTCOMES

The types of outcomes that result from medical care interventions can be described in a number of ways. One classic list, called the *five D’s*—death, disease, disability, discomfort, and dissatisfaction—captures a limited range of outcomes for use in assessing the quality of medical care.⁷ The *five D’s* do not reflect any positive health outcomes and, as a result, have little value in contemporary outcomes research.

A more comprehensive conceptual framework, the ECHO model, places outcomes into three categories: economic, clinical, and humanistic outcomes.⁸ As described by Kozma et al.,⁸ *economic outcomes* are the direct, indirect, and intangible costs compared with the consequences of a medical intervention. *Clinical outcomes* are the medical events that occur as a result of the condition and/or its treatment. 2 *Humanistic outcomes*, which now are more commonly called *patient-reported outcomes*,⁹ are the consequences of the disease and/or its treatment as perceived and reported by the patient.

Patient-reported outcomes (PROs) refer to a number of important outcomes, including self-assessed health status, symptom experience, treatment satisfaction, and functioning and perceived well-being. PROs are increasingly being used to complement safety data, survival rates, and traditional indicators of clinical efficacy in therapeutic intervention trials.¹⁰ PRO data may not only serve to complement clinical indicators of treatment efficacy; in some cases (e.g., pain), a PRO may be the only viable end point because there are no observable or measurable physical or physiological markers of disease or treatment activity.^{11,12} Willke et al.¹³ reviewed the effectiveness end points reported in U.S. Food and Drug Administration (FDA)-approved product labeling for new molecular entities approved from 1997 through 2002 and found that PRO end points were included in 30% (64) of the 215 product labels reviewed. For 23 of the products, PROs were the only end points reported. PROs were most commonly used as end points for antiinflammatory,

central nervous system, gastrointestinal, respiratory, allergic conjunctivitis, and urologic therapy areas.

The importance of PROs as end points in clinical trials was further underscored by the release of the FDA's (draft) guidance for industry titled *Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims*.¹⁴ The intent of the guidance was to describe how the FDA will evaluate the appropriateness and adequacy of PRO measures used as effectiveness end points in clinical trials. This issue has been the focus of a significant amount of attention during the past several years,^{15–19} and the guidance has been eagerly anticipated. The focus of this chapter is *health-related quality of life* as a patient-reported outcome of pharmacotherapeutic interventions.

HEALTH-RELATED QUALITY OF LIFE

DEFINITION

One of the essential elements of outcomes research is the assessment of *health-related quality of life*. It has been proposed that studies of health outcomes use the term *health-related quality of life* (HRQOL) to distinguish health effects from the effects of financial status, family life, friendships, job satisfaction, and other factors on overall quality of life.²⁰ Only health outcomes are discussed in this chapter, so *quality of life* and *health-related quality of life* are used interchangeably. In addition, although there can be a difference between self-reported *health status* (descriptive) measures and *HRQOL* (descriptive and evaluative) measures, that distinction may not always be made within the context of this chapter.

HRQOL CONTROVERSY

Some observers question whether, when completing HRQOL instruments, respondents are able to distinguish between the impact of health versus the impact of other important life domains on their functioning and well-being.

QOL, like other aspects of the human experience, is hard to define. In much of the empirical literature, explicit definitions of QOL are rare; readers must deduce the implicit definition of QOL from the manner in which it is measured. However, some authors have provided definitions. For example, Revicki et al.²¹ define HRQOL as “the subjective assessment of the impact of a disease and treatment across the physical, psychological, social, and somatic domains of functioning and well-being.” Patrick and Erickson²² propose that HRQOL is “the value assigned to duration of life as modified by the impairments, functional states, perceptions, and social opportunities that are influenced by disease, injury, treatment, or policy.” Although the two definitions differ in level of description, a conceptual characteristic they share is multidimensionality. Although the terminology may vary with the author, commonly measured domains of HRQOL include the following:

- Physical health and functioning
- Mental health and functioning
- Social and role functioning
- Perceptions of general well-being

Although spiritual well-being is receiving increasing attention,²³ it is not explicitly assessed in most general HRQOL measures. However, it is more likely to be assessed by HRQOL measures specifically developed for patients with diseases that can substantially impact both quality and quantity of life (e.g., cancer).²⁴

HRQOL CONTROVERSY

Should symptoms of a disease or the adverse effects of treatment interventions be explicitly assessed by HRQOL instruments? Although some instruments include items addressing specific symptoms (e.g., pain) or side effects, most HRQOL instruments are developed based on the premise that if a symptom or adverse effect is sufficiently problematic, it will be manifested in one or more of the measured HRQOL domains.

RELEVANCE OF QUALITY OF LIFE AS AN OUTCOME

For medical care providers, HRQOL increasingly is viewed as a therapeutic end point. An overriding factor leading to this has been the gradual shift in the focus of primary medical care from limiting mortality to limiting morbidity and the patient-reported impact of that morbidity. The pattern of illness in the United States has shifted from mostly acute disease to one in which chronic conditions predominate. In the early part of the 20th century, many individuals died of infectious diseases for which cures (e.g., antibiotics) or effective preventive measures (e.g., vaccines, improved sanitation) were unavailable or underused. Today, although many diseases may shorten life expectancy, more likely a disease will have adverse health consequences leading to dysfunction and decreased well-being. For those conditions that shorten life expectancy and for which there are no cures, managing symptoms and maintaining function and well-being should be the primary objectives of medical care.

Because therapeutic interventions such as medications have the potential to increase or decrease HRQOL, medical care providers must strive to achieve enhanced HRQOL as an outcome of therapy. Although it must be assumed that HRQOL has always played an implicit role in the provision of healthcare, it has not always been viewed as equal in importance to the more clinical or physiologic outcome parameters (e.g., blood pressure). The subjective nature of HRQOL assessment has made many people uneasy with it as a measure of the patient outcomes produced by medical treatment.²⁵

3 However, there is growing awareness that, in certain diseases, HRQOL may be the most important health outcome to consider in assessing treatment.²⁶ Physiologic measures may change without improving functioning and well-being. Likewise, patients may feel and function better without measurable change in physiologic values.

QUALITY OF LIFE AND PHARMACOTHERAPY

As described by Smith,²⁷ four possible QOL outcomes are associated with pharmacotherapy: (a) QOL is improved, (b) QOL is actively maintained, (c) QOL decreases, or (d) QOL remains unaffected. To effectively assess these possible outcomes, moving beyond consideration of only the biologic or physical manifestations of a disease or its treatment is essential. The use of standardized measurement tools (e.g., self-reported HRQOL instruments) to collect information regarding the impact of pharmacotherapy on the quality of patients' lives is increasing.²⁸ However, the vast majority of claims in prescription drug advertisements continue to be based on physiologic parameters and/or clinician-assessed physical function rather than patient-reported functioning and well-being.^{13,29}

A study by Croog et al.³⁰ was one of the first in a growing body of literature reporting the QOL impact of pharmacotherapy, specifically the use of antihypertensive agents. Along with hypertension, examples of other therapeutic areas that are receiving attention are asthma, cancer, diabetes, arthritis, human immunodeficiency virus (HIV)/acquired immune deficiency syndrome (AIDS), and depression.^{31–37} The type of condition and type of treatment dictate the importance of HRQOL data in determining the value of pharmaco-

TABLE 2-1 Taxonomy of Quality-of-Life Instruments

Generic instruments
Health profiles
Preference-based measures

Specific instruments
Disease specific (e.g., diabetes)
Population specific (e.g., frail older adults)
Function specific (e.g., sexual functioning)
Condition or problem specific (e.g., pain)

Data from Patrick DL, Deyo RA. *Med Care* 1989;27:S217–S232.

therapy. As discussed by Badia and Herdman,³⁸ in chronic conditions and palliative treatments (i.e., ameliorating symptoms but not curing the underlying disease), HRQOL may be the primary measure of efficacy. However, with acute conditions and curative treatments, HRQOL is likely to be secondary (although excluding it may underestimate the positive and negative impacts of the treatment).

4 Information about the impact of pharmacotherapy on QOL can provide additional data for making policy decisions on medication use. In fact, the Academy of Managed Care Pharmacy, in its *Format for Formulary Submissions*, states that manufacturers of pharmaceutical, biologic, and vaccine products should include outcomes data (e.g., QOL) in their formulary submission dossiers.³⁹ When available, pharmacy and therapeutics committees should incorporate QOL data into the formulary and practice guideline decision-making process. HRQOL as an input to clinical decision making at the patient level also is important. For example, alternative treatments may have equal efficacy based on traditional clinical parameters (e.g., blood pressure reduction) but produce very different effects on the patient's HRQOL. Thus, a provider's selection among competing alternatives may hinge on documented differential impact on HRQOL. A perceived decrease in QOL attributed by the patient to an adverse effect of the drug may lead to a decrease in adherence to the medication regimen.²⁷

MEASURING QUALITY OF LIFE

TYPES OF INSTRUMENTS

Hundreds of HRQOL instruments are available.^{40–42} Table 2–1 gives a taxonomy of the different types of instruments.⁴³ 5 A primary distinction among HRQOL instruments is whether they are generic or specific.

Generic Instruments

Generic, or general, HRQOL instruments are designed to be applicable across all diseases or conditions, across different medical interventions, and across a wide variety of populations.⁴⁴ Table 2–2 lists the dimensions or domains of five generic instruments. Although no longer commonly used, the Nottingham Health Profile (NHP)⁴⁶ and Sickness Impact Profile (SIP)⁴⁸ are included because of their historical significance to the field of health status and HRQOL assessment. In choosing or evaluating the use of an instrument, the specific dimensions of functioning and well-being covered must be considered. The instruments in Table 2–2 have common dimensions, but they also reflect the diversity and range of dimensions covered. The two main types of generic instruments are health profiles and preference-based measures.

Health Profiles

Health profiles provide an array of scores representing individual dimensions or domains of HRQOL or health status. An advantage of a health profile is that it provides multiple outcome scores that may be useful to clinicians and/or researchers attempting to meas-

TABLE 2-2 Domains Included in Selected Generic Instruments

EuroQol Group's EQ-5D⁴⁵	
Mobility	Self-care
Usual activity	Pain/discomfort
Anxiety/depression	
Nottingham Health Profile (NHP)⁴⁶	
Part I: Distress within the following domains	
Emotions	Energy
Sleep	Pain
Social isolation	Mobility
Part II: Health-related problems within the following domains	
Occupation	Sex life
Housework	Hobbies
Social life	Holidays
Home life	
Quality of Well-Being Scale (QWB)⁴⁷	
Symptoms/problems	Physical activity
Mobility	Social activity
Sickness Impact Profile (SIP)⁴⁸	
Sleep and rest	Home management
Eating	Recreation and pastimes
Work	Body care and movement
Ambulation	Alertness behavior
Mobility	Emotional behavior
Communication	Social interaction
Health Utilities Index (HUI)—Mark III⁴⁹	
Vision	Dexterity
Hearing	Cognition
Speech	Pain and discomfort
Ambulation	Emotion

ure differential effects of a condition or its treatment on various QOL domains.

A commonly used profile instrument is the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36).⁵⁰ The instrument includes nine health concepts or scales (Table 2–3). The SF-36 can be self-administered or administered by a trained interviewer (face to face or via telephone). This instrument has several advantages. For example, it is brief (it takes approximately 5 to 10 minutes to complete), and its reliability and validity have been documented in many clinical situations and disease states.^{51,52} The SF-36 has provided a means of aggregating the items into physical (PCS) and mental (MCS) component summary scores.⁵³ In addition, an abbreviated version of the SF-36, containing only 12 items (SF-12), is available.⁵⁴ However, the scale scores and the MCS and PCS scores derived from the SF-12 are based on fewer items and fewer defined levels of health and, as a result, are estimated with less precision and less reliability. The loss of precision and reliability in measurement can be a problem in small samples and/or with small expected effect sizes for an intervention. An example of the use of SF-36 data in the labeling (i.e., prescribing information) for a biopharmaceutical product (thyrotropin alfa for injection) is available at http://www.thyrogen.com/healthcare/p_hc_overview.asp.

TABLE 2-3 SF-36 Scales and Number of Items per Scale (SF-36/SF-12)

Physical functioning (10/2)
Role limitations attributed to physical problems (4/2)
Bodily pain (2/1)
General health (5/1)
Vitality (4/1)
Social functioning (2/1)
Role limitations attributed to emotional problems (3/2)
Mental health (5/2)
Health transition (1/0)

Compiled from Ware and Sherbourne⁵⁰ and Ware et al.⁵⁴

Preference-Based Measures

HRQOL as assessed by preference-based measures is a single overall index score on a scale anchored by 1.0 (full health) and 0.0 (dead). Health states considered worse than dead can be reflected by negative numbers on the scale. This approach combines the measurement of an individual's health status with an adjustment for the relative desirability of, or preference for, that health state. The preferences are measured or assigned empirically through a variety of procedures. Although often called health state *utilities*, the term *preferences* is used in this chapter as the broader term because it subsumes both *utilities* and *values*.⁵⁵

Preference-based measures are useful in pharmacoeconomic research, specifically cost–utility analysis (CUA).⁵⁶ CUA, an economic technique discussed in Chapter 1, involves comparing the costs of an intervention (e.g., a medication) with its outcomes expressed in units such as quality-adjusted life years (QALYs) gained. QALYs gained is an outcome measure that incorporates both quantity and quality of life. This can be a key outcome measure, especially in diseases such as cancer, where the treatment itself can have a major impact on patient functioning and well-being. Numerous published studies have used CUA to evaluate the economic efficiency of healthcare interventions, including pharmaceuticals and medical devices. A review of CUAs published from 1976 to 2001 by Neumann et al.⁵⁷ found that the number of CUAs has increased markedly over that time and that the quality of studies is improving. CUA data compiled during this extensive review is available at www.tufts-nemc.org/cearegistry.

QALYs can be produced by increases in QOL and/or length of life. Fig. 2–1 represents a case in which QALYs were gained through an increase in QOL alone. The top curve represents the hypothetical life course of a cohort of individuals receiving a specific healthcare intervention compared with the life course of a cohort (i.e., lower curve) that did not receive the intervention. Average age at death did not differ between the two cohorts, but the intervention led to improvements in QOL in the treatment cohort. The area between the curves represents the QALYs gained through the intervention. This hypothetical case reflects a chronic disease, such as osteoarthritis, in which functioning and well-being are increased but survival remains unchanged. Other hypothetical combinations of quality and quantity of life can be graphed in this manner. For example, an alternative scenario could reflect a temporary decrease in QOL but an increase in survival that may result from a chemotherapeutic regimen for cancer.

HRQOL CONTROVERSY

Although the QALY is the most commonly used health outcome summary measure, it is not the only one. Other conceptually equivalent outcomes include *years of healthy life* (YHL), *well years* (WYs), *health-adjusted person years* (HAPYs), and *health-adjusted life expectancy* (HALE). An alternative concept called *healthy year equivalents* (HYEs) has been proposed as theoretically superior to QALYs, but its practical significance has been limited.

Direct Measures of Health State Preferences

The most commonly used direct measurement techniques include visual analog scales, standard gamble, and time trade-off.⁵⁸

Visual Analog Scales The visual analog scale (VAS) is a line, typically 10 to 20 cm in length, with the end points well defined (e.g., 0 = worst imaginable health state and 100 = best imaginable health state). The respondent is asked to mark the line where he or she would place a real or hypothetical health state in relation to the two end points. In addition, because death may not always be considered

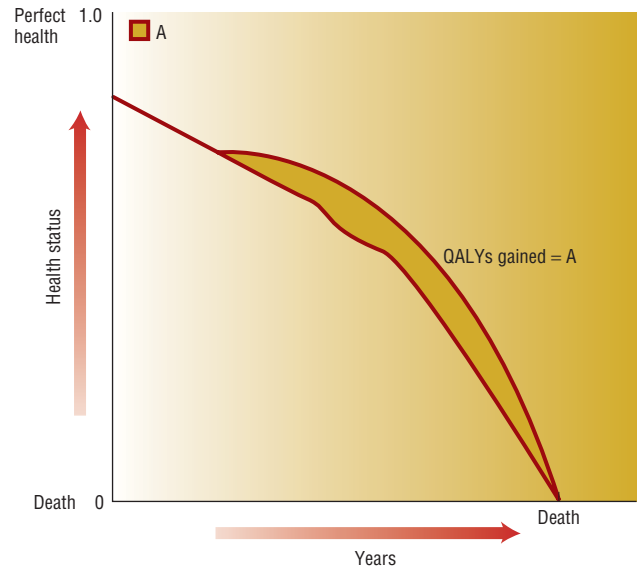


FIGURE 2-1. QALYs gained (i.e., area between the curves) as the outcome of a hypothetical healthcare intervention, such as a drug. (QALY, quality-adjusted life-year.)

the worst possible health state, the subject's placement of death on the scale in relation to the other health states must be explicitly elicited. If a subject has placed death at 0 and rates a health state at the midpoint between 0 and 100 on the scale, that subject's preference for that health state is 0.5.

Standard Gamble The standard gamble offers a choice between two alternatives: choice A, living in health state i with certainty, or choice B, taking a gamble on a new treatment for which the outcome is uncertain. Fig. 2–2 shows this gamble.⁵⁵ The subject is told that a hypothetical treatment will lead to perfect health, for a defined remaining lifetime, with a probability of p or immediate death with a probability of $1 - p$. The subject can choose between remaining, for the same defined lifetime, in state i , which is intermediate between healthy and dead, or taking the gamble and trying the new treatment. The probability p is varied until the subject is indifferent between choices A and B. For example, if a subject is indifferent between the choices A and B when $p = 0.75$, the preference (i.e., utility) of state i is 0.75.

Time Trade-Off Fig. 2–3 represents the time trade-off (TTO) technique for a chronic disease state.⁵⁵ Here, the subject is offered a choice of living for a variable amount of time x in perfect health or a defined amount of time t in a health state i that is less desirable. By reducing the time x of being healthy (at 1.0) and leaving the time t in the

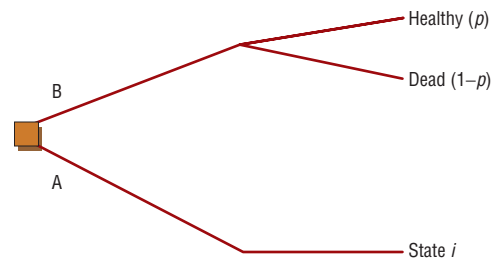


FIGURE 2-2. Standard gamble for a chronic health status. The subject is offered the choice between A and B. A involves the certainty of living in health state i (a suboptimal health state) for a specified period of time. B involves an intervention that could lead to full health for the same period of time or immediate death. The probabilities associated with the outcomes of healthy and dead are p and $1 - p$, respectively. As p is varied, the indifference point between choices A and B represents the utility of state i .

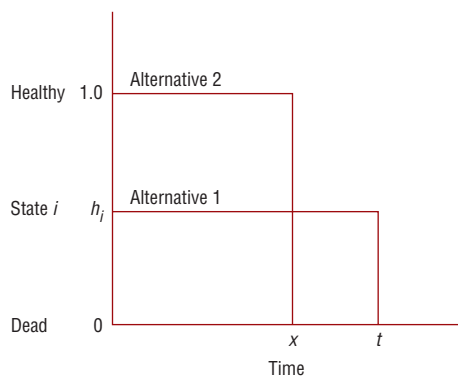


FIGURE 2-3. Time trade-off for a chronic health state. The subject chooses between living a varying amount of time in full health (x) and living a specified amount of time (t) in state i . The length of time in full health is shortened until the subject is indifferent between the two choices. The value of health state i (h_i) then is calculated by dividing x/t .

suboptimal health state fixed, an indifference point can be determined ($h_i = x/t$). For example, a subject may indicate that undergoing chronic hemodialysis for 2 years is equivalent to perfect health for 1 year. Therefore, the value of that health state would be 0.5 ($h_i = 1/2$).

HRQOL CONTROVERSY

There is considerable debate regarding the best approach to the direct measurement, or elicitation, of health state preferences. The empirical literature consistently shows that there are differences in the preferences derived through the different elicitation methods. Although there have been calls for the development of standardized preference elicitation protocols, the lack of consensus likely will continue into the foreseeable future.

Multiattribute Health Status Classification Systems

In addition to direct measures, instruments are available for which the health state preferences have been derived empirically through population studies. The instruments are administered to assess respondents' health status or health state, which then is mapped onto a multiattribute health status classification system. Examples of such instruments include the Quality of Well-Being Scale (QWB),⁴⁷ the Health Utilities Index (HUI),⁴⁹ the EuroQol Group's EQ-5D,⁴⁵ and the SF-6D.⁵⁹ Although each is described briefly below, more thorough descriptions of these four instruments are provided elsewhere.^{60,61}

The QWB is a generic HRQOL instrument that includes symptoms or problems plus three dimensions of functional health status (see Table 2–2). Standardized preference values for the health states represented by the QWB have been measured (via the category rating scale method, a technique related to VASs) and validated on a general population sample.⁴⁷ The QWB was available originally only as an interviewer-administered version, but a self-administered version now is available.⁶²

The HUI is another generic instrument that describes the health status of a person at a point in time in terms of his or her ability to function on a set of attributes or dimensions of health status. The HUI Mark II/III is available as a 15-item self-administered form. The measurements for the development of the health state preference system were made with VASs and the standard gamble technique. The dimensions covered in the most recent version of the HUI (Mark III) are listed in Table 2–2.⁴⁹

The EQ-5D was designed to be self-administered and short enough to be used in conjunction with other measures.⁴⁵ The first of two parts classifies subjects into one of 243 health states within five dimensions. A set of TTO-based preference weights derived

from the general U.S. adult population now is available for the 243 EQ-5D health states.⁶³ The second part of the EQ-5D is a 20-cm VAS that has end points labeled “best imaginable health state” and “worst imaginable health state” anchored at 100 and 0, respectively. Respondents are asked to indicate how they rate their own health state by drawing a line from an anchor box to that point on the VAS that best represents their own health on that day.

With the dominance of the SF-36 among the profile measures, there was significant interest in deriving a health index score from it to enable its incorporation into economic evaluation involving QALYs. In order to address this limitation, Brazier et al.⁶⁴ undertook the development of a preference-based index that used health state classifications derived from the SF-36 items. The resulting multiattribute health status classification system is called the SF-6D.⁵⁹ The current version of the SF-6D is based on 11 SF-36 items. With four to six levels for each of six dimensions, it defines 18,000 possible health states. A UK general population study was conducted to elicit preferences for a sample of the SF-6D health states using a standard gamble technique. A model then was constructed for estimating mean preferences for all possible SF-6D health states.

HRQOL CONTROVERSY

Whose preferences should be used in the calculation of QALYs for CUA? Some authors have argued that health state preferences elicited from the general population should not be applied to specific patient groups. However, when public resource allocation decisions are being made, general population preferences may be the most appropriate.

Specific Instruments

Specific or targeted instruments are intended to provide greater detail concerning particular outcomes, in terms of functioning and well-being, uniquely associated with a condition and/or its treatment. Several selected examples of disease-specific instruments are listed in Table 2–4; however, hundreds of other targeted instruments are available.^{40–42} One of the instruments listed is the Asthma Quality-of-Life Questionnaire (AQLQ), a 32-item instrument developed to assess the impact of asthma on patients' everyday functioning and well-being.⁶⁶ Results from research in which the AQLQ was used have appeared in promotional materials for the salmeterol inhaler (GlaxoSmithKline). As opposed to prior prescription drug advertisements that involved predominantly physiologic-based QOL claims,²⁹ this was one of the first times a pharmaceutical firm has promoted a product based on data from trials involving QOL as a primary outcome measure. This is likely to occur with increasing frequency as pharmaceutical firms look for ways to demonstrate value and differentiate their products from those of the competition.^{17,21} Leidy et al.⁷¹ have provided useful recommendations for evaluating the validity of QOL claims for labeling and promotion of pharmaceuticals. Disease- or condition-specific instruments can, although not always, be more sensitive than a generic measure to particular changes in HRQOL secondary to the disease or its treatment. In addition, specific measures may appear to be more clinically relevant to patients and healthcare providers.⁴³

TABLE 2-4 Selected Disease-Specific Quality-of-Life Instruments

Arthritis Impact Measurement Scales (AIMS) ⁶⁵
Asthma Quality-of-Life Questionnaire (AQLQ) ⁶⁶
Functional Assessment of Cancer Therapy—Colorectal (FACT-C) Scale ⁶⁷
Kidney Disease Quality-of-Life (KDQOL) Instrument ⁶⁸
Quality of Life in Epilepsy (QOLIE) ⁶⁹
Medical Outcomes Study HIV Health Survey (MOS-HIV) ⁷⁰

However, a concern regarding the use of only specific instruments is that by focusing on the specific impact, the general or overall impact on functioning and well-being may be overlooked. In studies involving pharmacotherapy, the use of both a generic and a specific instrument may be the best approach. The generic instrument provides a more general outcome assessment and allows comparability across other disease states or conditions in which it has been used. An appropriately selected specific instrument should provide more detailed outcome information regarding expected changes in the particular patient population.

MEASUREMENT ISSUES

A number of issues must be considered when evaluating existing HRQOL research and/or choosing the appropriate instrument to use when designing a study involving QOL assessment. A thorough review of these issues is not within the scope of this chapter; more in-depth reviews of methodologic considerations are available in the literature.^{22,72,73} **6** Of particular concern are the psychometric properties of a chosen instrument. *Psychometrics* refers to the measurement of psychological constructs, such as HRQOL. Instruments should be developed and tested such that one can place confidence in the measurement made. Psychometric properties of measures (e.g., reliability and validity) are considered in the review criteria developed by the Scientific Advisory Committee of the Medical Outcomes Trust (MOT).⁷⁴ The MOT is a depository and distributor of standardized health outcomes measurement instruments. Every instrument that is proposed for addition to the MOT list of approved instruments is reviewed against a rigorous set of eight attributes. These attributes provide a useful evaluative framework. The eight attributes of an instrument addressed by the review criteria are as follows: (a) conceptual and measurement model, (b) reliability, (c) validity, (d) responsiveness, (e) interpretability, (f) respondent and administrative burden, (g) alternate forms, and (h) cultural and language adaptations.

Conceptual and Measurement Models

A *conceptual model* is the rationale for and description of the concepts that a measurement instrument is intended to assess and the interrelationships of those concepts. A *measurement model* is an instrument's scale and subscale structure and the procedures followed to create scale and subscale scores. An example is the well-defined conceptual and measurement models for the scales and scale structure of the SF-36.⁷⁵ The SF-36 contains 36 items that cover nine theory-based health concepts. Eight of these health concepts are measured by multiitem scales. There is a clearly defined means of creating the individual scale scores and the PCS and MCS scales.⁵³

Reliability

Reliability refers to the extent to which measures give consistent or accurate results. The purpose of evaluating the reliability of a HRQOL instrument is to estimate how much of the variation in a score is real as opposed to random. The two reliability assessment methods discussed most often in the HRQOL literature are internal consistency and test–retest reliability. *Internal consistency* is an assessment of the performance of items within a scale. It is a function of the number of items and their covariation.⁷⁶ Internal consistency is commonly measured using the Cronbach α -coefficient. α -Coefficients >0.90 are recommended for making comparisons between individuals and >0.70 for comparisons between groups.⁷⁷

Test–retest reliability refers to the relationship between scores obtained from the same instrument on two or more separate occasions when all pertinent conditions remain relatively unchanged. It is usually evaluated using the intraclass correlation coefficient

(ICC).⁷³ However, HRQOL is not assumed to be constant over the course of time. In fact, most clinical studies attempt to assess how HRQOL changes. Test–retest reliability estimates may have limited value in evaluating measures that are designed to assess a dynamic process.

Interrater reliability and *equivalent-forms reliability* are two other approaches to reliability assessment that are not used as commonly in HRQOL research. More in-depth discussions of these and the other reliability assessment methods are found elsewhere.^{73,78}

Validity

Reliability is necessary but not sufficient for valid measurement.⁷⁶ *Validity* is an estimation of the extent to which the instrument is measuring what it is supposed to be measuring. Validity is not an absolute property of an instrument. Hence, a measurement instrument is not “valid,” but empirical data can provide evidence to support its validity. Three types of validity commonly considered are criterion, content, and construct.

Criterion validity is demonstrated when a new measure corresponds to an established measure or observation that accurately reflects the phenomenon of interest. By definition, the criterion must be a superior measure of the phenomenon if it is to serve as a comparative norm. However, in HRQOL assessment, “gold standards” or criterion measures rarely exist against which a new measure can be compared.

Content validity, which is infrequently tested statistically, refers to how adequately the questions/items capture the relevant aspects of the domain or concept being measured.

Construct validity refers to the relationship between measures purporting to measure the same underlying theoretical construct (convergent evidence) or purporting to measure different constructs (discriminant evidence). For example, convergent evidence for the validity of a new measure of emotional well-being could be established by showing a strong association between the new scale and the Beck Depression Inventory.⁷⁹ Evidence for the construct validity of other aspects of the measure might be established through comparisons with physiologic measures, organ pathology, or clinical signs.

Responsiveness

Responsiveness, or sensitivity to change, is the ability or power of the measure to detect clinically important change when it occurs.⁸⁰ Although some authors have suggested that responsiveness is a psychometric property of a measure distinct from validity,⁸¹ others argue that responsiveness is an aspect of validity rather than a separate property.^{76,82}

HRQOL CONTROVERSY

What constitutes a minimally important difference on an HRQOL measure? Although the statistical significance of a change or difference score is often used to denote important change, it may overestimate or underestimate the true impact of the disease and/or its treatment in terms of change that is perceptible and important to patients. Discussions regarding the concept of minimally important difference are increasingly appearing in the literature.

Interpretability

Interpretability is the degree to which one can assign qualitative meaning to an instrument's quantitative scores. Interpretability is facilitated by comparison of a score or change in scores to a qualitative category that has clinical or commonly understood meaning. For example, it would be helpful to know how scale scores

obtained in a specific patient sample compare with the scale scores of the general population. Ware et al.⁷⁵ have provided very useful U.S. population-based normative data for the SF-36.

Respondent and Administrative Burden

Respondent burden refers to the time, energy, and other demands placed on those to whom the instrument is administered. *Administrative burden* refers to the demands placed on those who administer the instrument. A practical aspect of the measurement of HRQOL is length of the instrument or the administration time involved. Instruments should be as brief as possible without severely compromising the validity and reliability of the measurement. The longer an instrument, the greater is the respondent burden. This can lead to an individual's unwillingness or refusal to complete the instrument or to incomplete responses.

Alternate Forms

Alternate forms of an instrument include all modes of administration other than the original source instrument. Evidence should be provided that supports the comparability of the alternate mode of administration with that of the original instrument.⁸³ Many HRQOL measures can be administered in different ways. The primary modes of administration are (a) self-administered or (b) interviewer-administered questionnaires, either in person or over the telephone.⁴³ However, electronic (ePRO) modes of self-administration (e.g., palmtops, touch screens, interactive voice response systems, Web-based questionnaires) are becoming increasingly important.⁸⁴ Used but not recommended are proxy responders (i.e., using a healthcare provider, family member, or friend to respond for the subject when the subject is unable to complete the instrument). Because HRQOL is such a subjective concept, patients must have the opportunity to provide their perspective on the impact of illness and/or medical care on their functioning and well-being. The patient's perspective has been shown to be quite different from that of outside observers, including physicians, family members, or others close to the patient.⁸⁵

Cultural and Language Adaptations

Methods used to achieve conceptual and linguistic equivalence of cross-culturally adapted instruments should be explicitly stated.⁸⁶ Evidence should be provided that the measurement properties of the adaptation are comparable with those of the original instrument. This is an extremely important issue when planning cross-national QOL assessment projects. However, it also is very important within countries that are multicultural, such as the United States.⁸⁷ Many of the English-language instruments have been developed for the dominant U.S. culture and may not be appropriate for all patients.

OTHER MEASUREMENT ISSUES

Selection of an Appropriate Instrument

It is essential that the purpose of the measurement be well defined before selection of an HRQOL instrument. Is the purpose of the measurement to describe the health status or HRQOL of a patient population at a particular time or over time?⁸⁸ Is it to document change in health outcomes associated with a particular intervention? These and other questions should be answered before HRQOL instruments are selected. Too many practitioner-researchers attempting to demonstrate improvements in outcomes resulting from a pharmaceutical product or service select a commonly used generic instrument, such as the SF-36, with the expectation that it will be sufficiently responsive to changes that may occur. The best

approach may be to use the SF-36 or other generic instrument in conjunction with a more targeted, disease-specific instrument.

Availability of Instruments

Many HRQOL instruments are in the public domain. Although they can be used for no or little cost, a fee may be associated with the purchase of a user's guide or scoring manual. The MOT (www.outcomes-trust.org) is a source for a number of instruments, including the Duke Health Profile, QWB, MOS-HIV Health Survey, Migraine-Specific Quality of Life (MSQOL), and SIP. For information on availability of the SF-36 and SF-12, go to www.sf36.org. The FACIT (Functional Assessment of Chronic Illness Therapy) Web site (www.facit.org) provides an extensive array of cancer- and chronic disease-targeted instruments. Developers of particular instruments often can be contacted through addresses provided in other books referenced at the end of this chapter.⁴⁰⁻⁴²

CONCLUSIONS

The concept of HRQOL has gained increasing attention in the evaluation of the outcomes associated with medical care, including pharmacotherapy. In fact, in certain diseases, HRQOL may be the most important outcome to consider in assessing the effectiveness of healthcare interventions. Healthcare practitioners and policy-makers must remember that efforts to increase length of life must not outstrip the ability to maintain or improve QOL.

HRQOL assessment is a relatively new field of endeavor, and a number of theoretical and methodological issues remain unresolved. However, some general concepts in the measurement of HRQOL outcomes should be considered carefully when designing a study, evaluating existing research, or evaluating new programs or services. This chapter has provided only a brief overview of the concepts in an effort to sensitize students and healthcare practitioners to the importance of the area as well as to provide insight as to how these concepts can and should be incorporated into their practices.

ABBREVIATIONS

AIDS:	acquired immune deficiency syndrome
AQLQ:	Asthma Quality-of-Life Questionnaire
CUA:	cost-utility analysis
ECHO:	economic, clinical, and humanistic outcomes
FACIT:	Functional Assessment of Chronic Illness Therapy
HALE:	health-adjusted life expectancy
HAPY:	health-adjusted person-year
HIV:	human immunodeficiency virus
HRQOL:	health-related quality of life
HUI:	Health Utilities Index
HYE:	healthy year equivalent
ICC:	intraclass correlation coefficient
MCS:	mental component summary scale of the SF-36
MOT:	Medical Outcomes Trust
PCS:	physical component summary scale of the SF-36
PRO:	patient-reported outcome
QALY:	quality-adjusted life-year
QWB:	Quality of Well-Being Scale
SF-36:	36-Item Short Form Health Survey

VAS: visual analog scale

WY: well year

YHL: years of healthy life

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