

An Introduction to Quality of Life Assessment in Oncology: The Value of Measuring Patient-Reported Outcomes*

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Abstract

This article provides an introduction to the concepts of quality of life (QOL) research, including the documented uses and benefits of patient-reported outcomes. Health-related QOL data have been useful in clinical care studies, clinical trials, and cost-effectiveness studies. In the area of cancer treatment, such health-related QOL data have been influential on treatment decisions and cancer care. In addition, this article addresses the challenges resulting from more frequent use of patient-reported outcomes by researchers and physicians. In particular, the impact of the response-shift phenomenon is examined, as well as the time pressure, clinical constraints, and sub-optimal communication skills that may hinder the transfer of information from patient to physician and/or researcher.

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The increased emphasis on accountability in healthcare coincides with the notable development and sophistication of evidence-based medicine.¹ Rather than relying on the informal assessments and preferences of medical

care providers, this discipline seeks objective and subjective assessments of the effectiveness of medical intervention on patient outcomes. Accordingly, methods that integrate patient-reported outcomes into treatment assessments are being used more frequently, and the prevalence of peer-reviewed journal articles reporting patient-reported outcomes research has expanded exponentially in the past 2 decades.²

Patients arguably have the best perspective on the impact of a treatment. They experience first-hand the obvious benefits and burdens of treatments. Perhaps more important, however, they are aware of the hidden benefits and costs of a treatment that may solidify or threaten stringent adherence to provider recommendations. Asking patients about their perspectives has the potential to yield clinically meaningful end points that are an integral part of clinical decision-making. Thus, patient-reported outcomes address the fundamental value of a treatment, over and above the treatment's effect on measurable objective parameters of health.

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The Concept of Quality of Life

The notion of quality of life (QOL) has developed considerably in the quarter of a century since the field's inception. In general, QOL research consists of 2 broad areas. One of these areas, led by medical outcomes researchers, focuses on health-

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related parameters, or health-related QOL; the other area, led by medical sociologists, focuses on broader determinants of well-being, including sociological and economic determinants. This paper will focus on health-related QOL, which involves a broad-based and multidimensional construct. This construct incorporates the physical, psychological, and social functioning that are affected by the disease or treatment^{3,4} as well as existential aspects of QOL that relate to psychological well-being.^{5,6} Physical functioning is most commonly defined as the performance of or the ability to perform a range of activities of daily living, and it includes physical symptoms resulting either from the disease itself or from treatment. Psychological functioning ranges from severe psychological distress to a positive sense of well-being and may also encompass cognitive functioning. Social functioning refers to quantitative and qualitative aspects of social relationships and interactions and societal integration. Beyond this core set of health-related QOL domains, additional issues may be more relevant for specific groups of cancer patients, depending on the functional domains affected by the disease or treatment (eg, sexual functioning in patients undergoing mutilating surgery).

In addition to the more functional aspects of QOL, recent work has documented that existential or spiritual concepts have relevance to patients' symptom experience and are thus relevant for patient-reported outcome research. For example, clinical observation suggests that patients adjust their performance goals to accommodate cancer treatment-related toxicity.⁷ Some research suggests that patients with a stronger sense of coherence cope better with disability.⁸ Furthermore, patients who have a strong sense of meaning in life have been found to suffer from depression less often,⁹ and depressed patients have been found to be frequent users of healthcare with little apparent gain.¹⁰

Beyond measuring component domains, QOL measures often include a question about the patient's overall judgment of health and/or quality of life. Numerous

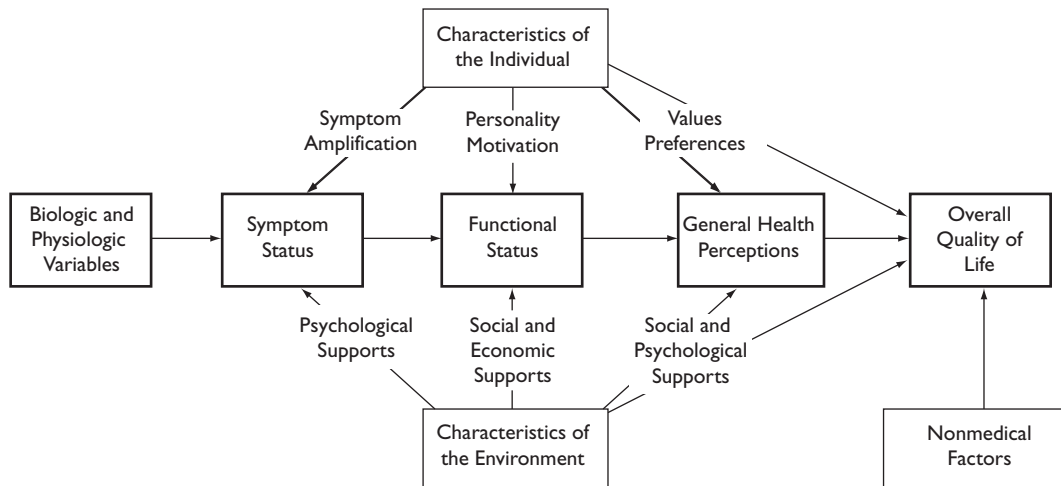
studies have documented that the whole is more than the sum of its parts, with a limited amount of the variance in global scores being explained by component scales.¹¹ Qualitative research on this global item suggests that the same frame of reference is not used by all respondents in answering the question, and that the specific referents vary by age, education, and race.¹¹ Thus, in making global QOL assessments, patients consider a broad range of domains and experiences.¹²

Health-related QOL is increasingly recognized as being subjective in nature, which frequently causes confusion and discomfort for clinicians. The term subjective, as opposed to objective, is not to imply that QOL is unreliable and poorly defined, because health-related QOL can be measured reliably and validly. Rather, this term is being used in reference to the sense of importance to the subject, and that patients should be the primary source of information regarding their health-related QOL.^{3,4} The subjectivity of health-related QOL will thus help clinicians to gain insight into the patients' perspectives of their diseases and treatments. Accordingly, the power and utility of QOL measures for clinical decision-making are related to this subjectivity.

Modeling the Link between Patient-Reported and Clinical End Points

The usefulness of QOL and symptom measures in understanding clinical indicators is elucidated by a conceptual framework developed by Wilson and Cleary.¹³ The model posits causal linkages between 5 different types of outcome measures: biological or physiological variables, symptoms, functioning, general health perceptions, and overall QOL (**Figure**).¹³ Biological or physiological variables are usually objective and are reflected by findings on assessment of the function of cells and organs; examples are blood glucose level, serum cholesterol level, or blood pressure. Such biological and physiological variables are usually assessed by instruments, not by self-report. Symptoms are patients' subjective perceptions of an abnormal physical or psychological state.

Figure. Relationships Among Measures of Patient Outcome in a Health-Related Quality of Life Conceptual Model



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Functioning refers to assessments of ability to perform specific tasks or functions, such as physical, social, emotional, and role functioning. Although these assessments are usually done by patients, they can also be observed and reported by others. General health perceptions are patients' global perceptions about their health and include the values patients attach to different symptoms or functional impairments. Finally, overall QOL is a measure of life satisfaction that may be unrelated to health. For example, overall QOL may be strongly influenced by factors such as an individual's economic and employment status, family situation, or the political environment.¹⁴ QOL is thus not entirely different from biological parameters, but can be placed on a continuum from least to most subjective.

State of the Science on the Value of Health-Related QOL

Health-related QOL research has documented some major achievements in the past 2 decades. Four main areas of contribution in oncology research that have distinct relevance to supporting high-quality

clinical-care delivery to cancer patients are described below.

To Assess Treatment Outcome and to Qualify Survival. Support for incorporating health-related QOL in cancer clinical trials is voiced by prominent clinical trial groups^{15,16} and national and international cancer institutes and societies.^{17,18} Although less opportunity is available for QOL assessment in phase I and II trials, it is increasingly assuming primary importance in phase III clinical trials, particularly in cases where significant differences in survival gain or tumor response are not to be expected. Health-related QOL may thus be most informative in trials of advanced stage cancer where different palliative treatments are compared with limited effects on survival gain and tumor response.^{19,20} Additionally, health-related QOL is relevant when survival is gained at the expense of major toxicity.

For special cases of clinical trials in which cost-effectiveness is considered, health outcomes are most commonly expressed in terms of quality-adjusted

life years (QALYs). Such QALYs adjust QOL by incorporating estimates of preferences or utilities (valued between 0.0 and 1.0) for each health state constituting survival (eg, period with post-treatment symptoms, recurrence-free period, period with presence of local recurrence, and distant metastases, respectively).²¹ An alternative approach that combines survival with health-related QOL is the quality-adjusted time without symptoms or toxicity (Q-TWiST). This Q-TWiST is a statistical analytic method that partials survival time into time without disease symptoms or treatment toxicity, time with symptoms and/or toxicity, and time spent in relapse.²² Recent extensions of the method have modified it to include patient-reported QOL measures and importance weights in the computation of QALYs.²³

To date, hundreds of clinical trials and cost-effectiveness studies have been conducted that included health-related QOL as end point. These trials examined a wide range of patients differing in type and localization of tumor, disease stage, and treatment modality. In a number of these trials, health-related QOL results legitimized the institution of the cancer treatment. For example, the US Food and Drug Administration (FDA) approved gemcitabine for pancreatic cancer and epoetin α for chemotherapy-induced anemia and fatigue on the basis of clinical trial-based health-related QOL data.²⁴

To Assess Late Problems. Although the survival rates of cancer patients largely depend on the specific type, location, and stage of the tumor at diagnosis, the long-term QOL may be affected by cancer therapies, whether they are surgical, systemic, or radiotherapeutic. A legitimate question is how patients fare after their initial treatment. To date, hundreds of studies have assessed the short- to long-term health-related QOL of cancer patients within more or less homogenous groups formed according to tumor site and/or treatment modality. A specific question is related to the long-term

health-related QOL of those who survived pediatric cancer.

Survival of childhood cancer has increased considerably over the past few decades because of improvements in treatment and care. Approximately 65% of children with cancer are expected to survive at least 5 years after their cancer diagnosis.²⁵ As a consequence, the objective of pediatric oncology is changing from mere survival gain to survival gain accompanied by a health-related QOL comparable to that of the survivor's peers. However, growing evidence indicates that different therapies adversely affect physical outcome in the long term.²⁵ Additionally, survivors may also experience problems with cognitive and academic achievements,²⁶ occupational or vocational accomplishments,²⁷ and psychosocial adjustment.^{28,29} The studies examining long-term psychosocial sequelae generally conclude that the majority of survivors do not fare poorly, but subgroups of patients who experience serious psychosocial problems can be identified.^{28,29} A recent systematic review of 20 studies, conducted by Eiser et al,³⁰ suggested that interview studies are more likely to document discrepancies between controls and cancer survivors on psychological morbidity, indicating that methodological flaws may need to be more stringently considered before making definitive conclusions about cancer survivors' psychological adaptation and health-related QOL.

To Predict Mortality. An important clinical question is related to the identification of parameters predictive of prognosis. Although traditionally tumor size is an important predictor, ample evidence indicates that health-related QOL indices independently predict survival. This finding is documented for patients with breast cancer,³¹⁻³³ melanoma,³⁴ lung cancer,³⁵⁻³⁷ colorectal cancer,³⁸ and prostate cancer,³⁹ as well as for heterogenous cancer patient samples.⁴⁰ In some of these studies, health-related QOL was found to be even more predictive of survival than known biologic prognostic factors.^{31,35-38} An important point to note is that a few other

studies did not find a significant relationship between health-related QOL and time to death.^{37,38} There is some dispute about the explanation of these contradictory findings. Butow et al⁴¹ argue that the nonsignificant findings may be due, in part, to methodological flaws, such as small or heterogenous samples, failure to control for cancer stage and severity of disease symptoms, and inappropriate use of statistical analyses. Conversely, Herndon et al⁴² reason that health-related QOL is a significant predictor of survival only if the available clinical measures provide an incomplete or imprecise prognostic profile, which they believe to be the case in most of the studies reporting positive findings. They report that poorer health-related QOL predicted significantly poorer survival. However, after adjustment for a range of clinical factors, the only health-related QOL domain that remained independently predictive of survival was self-reported pain. Their reasoning and findings do not discredit this line of research. However, their results also confirm that the detailed and refined health-related QOL information adequately reflects a patient's physical condition.⁴²

Because administering a health-related QOL questionnaire to patients is often easier and less costly than obtaining most of the biological and clinical values, health-related QOL is a good proxy measure for clinical status that can be an independent predictor of survival.⁴¹ Explanation of the prognostic value of QOL indicators may include early perception of subtle signs of disease progression by the patient or the physician and optimistic coping style of the patient. Additionally, health-related QOL might be indicative of patients' adherence to treatment and follow-up schedules and thus might be indirectly related to the disease process.⁴¹ Although future research is needed to further test the viability of these explanations, the results underscore the prognostic power of psychosocial variables.

To Support Transfer of Information.
Oncologists as well as patients are willing

to discuss a wide range of health-related QOL issues.⁴³ However, time pressure, clinical constraints, and suboptimal communication skills may prohibit such an exchange.⁴⁴ Standardized health-related QOL questionnaires are increasingly being used in daily clinical practice to identify issues of concern to individual patients and to facilitate the communication between physicians and patients.⁴⁵ A patient is typically asked to complete a health-related QOL questionnaire while waiting to see the treating physician. A computer immediately processes patient responses, producing a clearly interpretable summary highlighting the most prevalent problems. In some instances, responses provided at previous visits are also included in the overview, allowing detection of changes over time. This synopsis can then be used by the physician or patient during the subsequent clinic appointment. The effectiveness of such interventions, conducted in a wide range of noncancer healthcare settings, was recently reviewed.^{46,47} Based on 24 randomized trials, feedback to clinicians was found to enhance the identification of psychological problems, and, to a lesser extent, functional problems. Additionally, some evidence suggests that such feedback leads to an increase in diagnoses and health services utilization, although this feedback was not found to affect other aspects of care, such as the number of prescriptions or changes in treatment. Patient outcomes, such as health status and satisfaction with care, remained unaffected by these interventions. The authors pointed to the heterogeneity of the studies to explain, in part, these findings. For example, health-related QOL feedback was provided either before, during, or after a medical consultation. They call for more stringent evaluations of this type of intervention.

Future Directions

Trends in clinical quality assurance and scientific clinical research increasingly support the integration of patient-reported outcomes. Two directions in particular hold great promise for enhancing the

meaning and usefulness of patient-report-outcomes in both applications.

Patients Have Changed Their Perspective Over Time: Response Shift Phenomena. Articles documenting health-related QOL data may at times report paradoxical or counter-intuitive findings. For example, patients may report a stable health-related QOL over time, while their clinical health status deteriorates considerably.^{48,49} Additionally, cancer survivors, in general, report a level of health-related QOL comparable to that of healthy people.³⁰ In other studies, cancer patients under active treatment were found to report levels of health-related QOL not inferior to those of healthy individuals.^{48,50} The recurrent finding that cancer patients report higher levels of health-related QOL than their healthcare providers and significant others observe is also puzzling.^{51,52} Such findings might be interpreted as resulting from changes in patients' personal standards or values or changes in the conceptualization of health-related QOL over the course of the disease trajectory. These changes, which are inherent to the process of accommodating to the illness, are referred to as the "response shift."^{53,54}

Although response shift is not new from a clinical or intuitive perspective, it is a relatively new phenomenon from a methodological viewpoint.¹⁴ Shifting internal criteria, values, and conceptualization of life may render assessments completed over time incomparable. Because the units of comparison have changed, the comparison itself has lost its meaning. For example, in the context of treatment evaluations, response shifts may attenuate or inflate estimates of treatment effects if patients adapt to treatment toxicities or disease progression over time. More important, differences in health-related QOL across treatment arms may be jeopardized when response shift affects the treatment groups differentially.^{55,56} Random allocation to treatment arms does not solve this problem because treatments may still result in different levels and types of toxicities. Furthermore, relatively small gains in function and QOL

have significant value, whereas comparable declines in status may be less meaningful.⁵⁷ Assessing response shift may therefore be needed to obtain a valid and sensitive assessment of change over time.

By integrating measures of changes in internal standards, values, and conceptualization into research designs, response shift effects can be explicitly measured and taken into account. As this is a relatively new field, methods to assess the different components of response shift are now arising. Sprangers and Schwartz⁵⁶ have described a range of detection procedures, including individualized approaches,⁵⁸ qualitative methods,⁵⁹ preference-based techniques,⁶⁰ and design approaches.⁶¹ While not without methodological flow design approaches have provided valuable information in a number of clinical studies in oncology.^{55,62-65} These and other investigations are the first of an emerging line of research addressing explicitly the dynamic nature of health-related QOL.

When Statistically Significant Results Are Also Clinically Meaningful. If a clinical trial results in statistically significant changes in health-related QOL outcomes, the key question is the extent to which these results are clinically meaningful. Because statistical significance is dependent on sample size, a 1-unit change on a health-related QOL scale ranging from 0 to 100 may result in a $P < .001$ if the result is based on a large sample (eg, more than 1000 patients). Clearly, this finding would most likely be trivial. Lydick and Epstein⁶⁶ distinguished 2 approaches to establish clinical meaningfulness. The first cluster of approaches, termed distribution-based, relates the results to some measure of variability. For example, originating from the social sciences, Cohen⁶⁷ proposed the use of standardized mean scores or effect sizes, defined as the mean change score divided by the pooled standard deviation, or the standard deviation of that change. The guidelines to interpret effect sizes in the range of 0.2 standard deviation units as small, 0.5 as moderate, and 0.8 as large, have been widely adopted. The crit-

icism of this approach, however, is that the magnitude of effect sizes is sensitive to the variability, or the standard deviation, of the population under study. More important, the interpretation of the magnitude of change is not intuitively meaningful. The second series of measures, termed anchor-based approaches, incorporate a meaningful, external measure that is more clearly understood than health-related QOL scores themselves. For example, frequently-used approaches, such as the minimal clinically important difference^{68,69} and the subjective significance questionnaire (SSQ) approach,⁷⁰ correlate change over time with a patient's overall evaluations regarding the extent to which they improved, remained stable, or deteriorated. The method is critically dependent, however, on patient ability to indicate change validly. Evidence suggests that such transition scores reflect the current health-related QOL of the patient rather than the change in health-related QOL over time.⁷¹

Recent research has attempted to empirically test the relationship between the distribution- and anchor-based approaches. For example, Osoba et al⁷⁰ compared their SSQ approach with effect sizes.⁷⁰ Cohen's guidelines were confirmed in this study in that small, moderate, and large effect sizes coincided with the same magnitude of change as indicated by the SSQ ratings. Norman et al⁷² recently demonstrated that effect size and a minimum clinically important difference (MCID) provide equivalent information. Based on simulation data and 4 empirical studies, an MCID of 0.5 on a 7-point scale, a frequently reported finding,⁶⁹ nearly equaled an effect size of 0.5, as the standard deviation of the change scores was consistently near 1. Interestingly, they also found that larger effect sizes coincided with a larger proportion of patients benefiting from treatment (ie, the difference between the proportion improving and the proportion deteriorating in the treatment and control groups).⁷² Because this relationship was found to be approximately linear, the practical implication is

that an effect size can be translated into the proportion benefiting from treatment. These findings led Norman et al to conclude that the differences between distribution- and anchor-based approaches are perhaps more illusory than real.

Many different methods can be used to demonstrate meaningful or minimally important changes in health-related QOL outcomes, and no single approach is perfect. Although the findings of Norman et al are reassuring, individual methods and the convergence of the different methods require further validation. This point led Revicki et al⁷³ to advocate the use of multiple sources of evidence of clinical meaningfulness in the same study. Such studies, as well as clinicians' day-to-day use of health-related QOL measures, are hoped to ultimately lead to the sort of clear interpretability of health-related QOL results that has become common for most clinical parameters.

Conclusion

The past 3 decades have witnessed major improvements in health-related QOL research that has become increasingly accepted by the medical community and society at large. Health-related QOL research has helped define and draw attention to the human side of cancer treatment²⁴ and has influenced the treatment itself. Clinical trial-based health-related QOL data are increasingly being used for FDA-approved marketing. QOL assessments have not only been useful in clinical trials and cost-effectiveness studies, but have also pointed to physical, cognitive, and psychosocial areas where former pediatric cancer patients may experience serious problems, even years after diagnosis. Additionally, health-related QOL data have been found to be strong predictors of survival. Finally, health-related QOL data have proved to be useful in clinical care studies, particularly in stimulating physician-patient communication of psychosocial issues. Health-related QOL studies thus yield relevant results that inform both physicians and patients and help them explicitly weigh the costs and benefits of different treatment

options, thus contributing to treatment decisions and cancer care. Although this research line has many achievements, it also faces a number of challenges. Response shift phenomena and clinical significance are promising directions for future research that are likely to enhance the sensitivity and relevance of QOL research to clinical care delivery.

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