Quality of Life

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Introduction

Over the past 40 years, quality of life has emerged as an important outcome for evaluating the impact of cancer across the continuum of care. With improvements in early detection and advances in diagnosis and treatment, more and more people are surviving cancer and living longer. The National Cancer Institute (NCI) estimates that at least 16.9 million Americans were living with a history of cancer in January 2019, and the current 5-year survival rate is 69%, up from 49% in the 1970s [1]. Whereas survival time or *quantity* of life was an early and important objective indicator of treatment success, *quality* of life has proven to be a recent and meaningful subjective complement to the survival benefits derived from treatments. Weighing survival vs. quality of life benefits is a critical part of medical decision-making for cancer patients [2], and measuring quality of life has thus taken on added significance. Accordingly, in 2009, the Food and Drug Administration (FDA) coined the term "patient-reported outcomes" (PROs) as "measurement of any aspect of a patient's health status that comes directly from the patient" (e.g., quality of life) and proposed criteria for selecting and integrating HRQOL PRO measures into therapeutic clinic trials [3].

Given the subjective nature of quality of life, efforts to operationalize the construct have led to multiple, overlapping definitions. The World Health Organization defined quality of life as an "individual's perception of their position in life in the context of the culture and value systems in which they live and in relation to their goals, expectations, standards and concerns. It is a broad-ranging concept affected in a complex way by the persons' physical health, psychological state, level of independence, social relationships, and their relationship to salient features of their environment" [4]. Others have noted the importance of the subjective comparison between an individual's current level of functioning or well-being and their expected level of functioning or well-being to their perceived quality of life [5]. For the purposes of this chapter, we are primarily concerned with health-related quality of life (HRQOL), defined as the extent to which one's usual or expected physical, mental, and social well-being are affected by a medical condition or its treatment [6, 7]. Collectively, these definitions highlight two critical aspects of HRQOL: (1) patients' subjective judgment of their well-being and (2) the multiple dimensions of HRQOL.

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Assessing Health-Related Quality of Life with Patient-Reported Outcomes

HRQOL is Multidimensional HRQOL can be examined using a global evaluation (a single question rating the patient's overall perception of HRQOL) or a total score (summary of sub-domain scores), and many HRQOL PROs include these overall assessments. Multiple sub-domains of HRQOL have been proposed within the literature. An earlier review found over 30 different names for HRQOL dimensions [8]. This same review suggested that seven HRQOL dimensions were independent contributors to overall HRQOL: physical concerns (symptoms, pain, etc.), functional ability (activity), family well-being, mental well-being, treatment satisfaction, sexuality (including body image), and social functioning.

More recently, three or four dimensions of HRQOL have been proposed as adequate to fully describe HRQOL: physical, mental, social, and, in some cases, spiritual [9]. The physical domain refers to perceived physical function (e.g., ease of walking without assistance) and physical symptoms (e.g., pain, nausea, and fatigue). The mental domain refers to positive and negative mood and other emotional symptoms. The social domain measures relationships with friends and family, enjoyment of social activities, and sexuality. The spiritual domain refers to the degree to which an individual finds comfort in their spiritual beliefs when coping with illness.

Levels of Measurement Because HRQOL is a multidimensional construct, the level of measurement selected for assessing HRQOL in cancer patients and survivors must be carefully considered. HRQOL in cancer patients and survivors can be organized conceptually under broad domains of generic and cancer-specific concepts. Generic concepts include global evaluations of HRQOL, as well as the commonly used dimensions of physical (symptoms and function), mental (affect, behavior, cognition), and social (relationships and function) HRQOL. Cancer-specific concepts include both disease- and treatment-specific measures of HRQOL. While this framework provides a useful model for conceptualizing the hierarchical relationships among various dimensions of HRQOL, it does not readily capture the number and type of HRQOL questionnaires available for use with cancer patients and survivors. These questionnaires can be appropriately grouped within generic and cancer-specific domains, but within each of these domains, there is much overlap of the physical, mental, and social dimensions, and thus they resist simple categorizations. Table 24.1 provides

Table 24.1 Measures of HRQOL used in patients with cancer and survivors

Generic
Medical Outcomes Study 36-Item (SF-36) & 12-Item (SF-12) Short-Form Health Surveys [147–149]
Patient-Reported Outcome Measurement Information System (PROMIS) [22, 49]
Nottingham Health Profile (NHP) [150]
Psychological Adjustment to Illness Scale – Self Report (PAIS-SR) [151]
Sickness Impact Profile (SIP) [152]
Spitzer Quality of Life Index (QL-I) [153]
Cancer-Specific
Cancer Rehabilitation Evaluation System (CARES) [154, 155]
European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-CORE 30 (EORTC QLQ-C30) [156]
Functional Assessment of Cancer Therapy-General, Version 4 (FACT-G) [17]
Functional Living Index-Cancer (FLIC) [157]
McGill Quality of Life Questionnaire-Revised (MQOL) [158, 159]
Quality of Life Index-Cancer Version III (QLI-CV III) [160]
Cancer Problems in Living Scale (CPILS) [161]
Impact of Cancer version 2 (IOCv2) [162, 163]
Long Term Quality of Life Scale (LTQL) [164–166]
Quality of Life in Adult Cancer Survivors (QLACS) [167]
Quality of Life - Cancer Survivors (QOL-CS) [168, 169]
Disease-Specific
EORTC modules: brain cancer (QLQ-BN20) [170], breast cancer (QLQ-BR23) [171], cervical cancer (QLQ-CX24) [172], colorectal cancer (QLQ-CR38) [173], endometrial cancer (QLQ-EN24) [174], head and neck cancer (QLQ-H&N35) [175], lung cancer (QLQ-LC13) [176], multiple myeloma (QLQ-MY24) [177], oesophago-gastric cancers (QLQ-OG25) [178], ovarian cancer (QLQ-OV28) [179], pancreatic cancer (QLQ-PAN26) [180] and prostate cancer (QLQ-PR25) [181]

Table 24.1 (continued)

FACT modules: breast cancer (FACT-B) [182], bladder cancer (FACT-Bl), brain cancer (FACT-Br) [183], colorectal cancer (FACT-C) [184], cancer of the central nervous system (FACT-CNS), cervical cancer (FACT-Cx), esophageal cancer (FACT-E) [185], endometrial cancer (FACT-En), gastric cancer (FACT-Ga), head and neck cancer (FACT-H&N) [186], hepatobiliary cancer (FACT-Hep) [187], lung cancer (FACT-L) [18], leukemia (FACT-Leu) [188], lymphoma (FACT-Lym) [189], melanoma (FACT-M) [190], multiple myeloma (FACT-MM), nasopharyngeal cancer (FACT-NP) [191], ovarian cancer (FACT-O) [192], prostate cancer (FACT-P) [193], and vulvar cancer (FACT-V) [194]
UCLA Prostate Cancer Index (UCLA PCI) [195]
HNQoL (Head and Neck Quality of Life Instrument [196]
Lung Cancer Symptom Scale (LCSS) [197]
Quality of Life -Breast Cancer (QOL-BC) [169, 198]
Colorectal Cancer-Specific Scale [199]
Symptom and Treatment Specific
McCorkle and Young Symptom Distress Scale (SDS) [200, 201]
M.D. Anderson Symptom Inventory (MDASI) [202]
Edmonton Symptom Assessment Scale (ESAS) [203]
Memorial Symptom Assessment Scale (MSAS) [204]
Rotterdam Symptom Checklist [205]
Symptom Checklist 90 (SCL-90) [206]
Brief Symptom Inventory (BSI) [207, 208]
Brief Fatigue Inventory (BFI) [209]
Brief Pain Inventory (BPI) [210]
Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) [55, 56]
National Comprehensive Cancer Network (NCCN)/ FACT symptom indices: bladder cancer (NFBISI-18), brain cancer (NFBrSI-24) [211], breast cancer (NFBSI-16) [212], colorectal cancer (NFCSI-19), head and neck cancer (NFHNSI-22), hepatobiliary cancer (NFHSI-18), kidney cancer (NFKSI-19) [213], lung cancer (NFLSI-17) [214], ovarian cancer (NFOSI-18) [215], prostate cancer (NFPSI-17) [216] and lymphoma (NFLymSI-18) [217]
Pediatric Measures
Miami Pediatric Quality of Life Questionnaire (MPQOLQ) [218]
Minneapolis–Manchester Quality of Life Form (MMQL) [219, 220]
PedsQL Cancer Module [221–224]
Pediatric Oncology Quality of Life Scale (POQOLS) [225, 226]
Pediatric PRO-CTCAE [63, 64]
Pediatric PROMIS [32, 35, 36]

a list of several frequently used PROs for HRQOL, as well as several promising new PROs for assessing HRQOL.

Selecting Measures Since there is no gold standard when it comes to measuring HRQOL, selecting an appropriate PRO measure can be a challenge, because there are numerous options available. When selecting a measure of HRQOL, researchers and clinicians should consider the reliability, validity, and responsiveness of the PRO instrument. Reliability is primarily concerned with the stability and reproducibility of a measure over time. Reliability is a necessary but not sufficient condition for the validity of a measure. Validity refers to an instrument's ability to accurately measure what it claims to measure. Several types of validity can be considered when evaluating the relative strengths of a measure with content, criterion, and construct validity among the most common. Finally, the responsiveness or sensitivity of a measure is the ability of the measure to differentiate between groups of patients expected to provide different HRQOL scores as a result of disease or treatment characteristics.

Measurement properties like reliability, validity, and responsiveness are important to consider when choosing any measurement tool. For HRQOL, however, a clinician or researcher must also consider dimensional or aggregated assessment. There has been some debate as to whether dimensional assessment (i.e., separate scores for each dimension, evaluated independently) or aggregated assessment (i.e., evaluation of only the total HRQOL score incorporating all four dimensions) is most clinically relevant. While dimensional assessment gives a richer and more detailed picture of HRQOL, and is often preferred by clinicians, aggregated scores may be more meaningful in areas such as clinical trials research in order to enable decisions to be made adjusting survival time for its quality [10] or in population health surveillance research in order

to inform global assessments of health status, facilitate subgroup comparisons, and track patterns and trends [11, 12].

Dimension scores provide more nuanced data than an aggregated score, but also have differential sensitivity to various cancer symptoms. For instance, compared with physical scales (e.g., physical functioning, functional ability, sexuality, etc.), psychosocial scales, such as mental well-being and social functioning, are less sensitive to changes in performance status or other primarily physical ratings. Psychosocial dimension scales are also less sensitive to disease-related characteristics, such as stage and type of disease [13, 14]. Several studies have found that the EORTC is unable to detect change in performance status rating or extent of disease [15, 16], and similar findings have emerged for the FACT measurement system [17, 18].

These findings make logical sense in the context of research suggesting that mental well-being may be no different in individuals diagnosed with cancer and those without cancer [19, 20]. It should be noted, however, that this finding has not always been replicated in all disease types and stages of illness (e.g., Lee et al) [21]. When the physical components of well-being are evaluated alongside measures of mental well-being, the relationship between the two is modest [9]. The fact that earlier and less refined measures of HRQOL may not adequately measure psychological distress is precisely due to the fact that these measures are comprised largely of physical symptoms such as nausea, appetite, and sleep.

In summary, if focusing on aggregate HRQOL scores only, the significant impact of cancer on any one dimension of HRQOL may be obscured. Including more targeted disease or treatment-specific measures along with general measures of HRQOL will permit comparisons across diseases while allowing for a level of sensitivity to issues or symptoms arising from a given disease or treatment. In addition, including multiple measures enhances the breadth of content coverage which may maximize one's ability to identify the efficacy of a treatment or intervention on HRQOL outcomes. A useful strategy is to select the measure most closely aligned with study objectives, confirm the relevant psychometric properties, and augment the selected measure(s) with a few additional questions targeted to the condition, disease, or treatment under study. Two recently developed measurement systems, the Patient-Reported Outcome Measurement Information System (PROMIS)® and the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE), provide the necessary psychometric rigor, breadth, precision, and flexibility for optimal assessment of a variety of HRQOL domains.

Patient-Reported Outcomes Measurement Information System (PROMIS)® The PROMIS is a National Institutes of Health (NIH) Roadmap initiative designed to improve PROs using state-of-the-art psychometric methods (see https://www.healthmeasures.net/explore-measurement-systems/promis). The PROMIS domain framework is informed by the World Health Organization's tripartite model of physical, mental, and social health but is further divided into a variety of symptom, affective, and interpersonal item banks (Fig. 24.1). PROMIS includes over 300 measures of physical, mental, and social HRQOL from 102 adult and 25 pediatric domains [22]. PROMIS has developed and calibrated measures to capture multiple areas of health and functioning [23–31] and has extensive evidence of its validity and reliability in both pediatric and adult cancer populations [32–39].

The PROMIS approach involves iterative steps of comprehensive literature searches, the development of conceptual frameworks, item pooling, qualitative assessment of items using focus groups and cognitive interviewing, and quantitative evaluation of items using techniques from both classical test theory and item response theory (IRT) [33, 40–44]. PROMIS is the most ambitious attempt to date to apply IRT models to HRQOL assessment. IRT is an alternative to classical test theory and models the likelihood that a person at a specific latent trait or symptom level

will respond to an item in a particular way [45–48]. Based upon one's overall pattern of responses to measure items, IRT modeling can produce a more precise estimate of a particular symptom or domain of HRQOL. This information can then be used to evaluate the quality of individual items, calibrate test scoring, and develop item banks for HRQOL domains. An item bank is comprised of carefully calibrated questions that can be used for item comparison and selection.

Calibrated item banks help set PROMIS apart from other established HRQOL measures and permit the application of computerized adaptive testing (CAT) tools, thus enabling tailored individual assessment while maintaining measurement precision and content validity. Other established HRQOL measures have a limited number of questions to assess each HRQOL construct (e.g., 5 questions on physical functioning, 8 questions on fatigue). PROMIS item banks (one bank for each PRO) include a much larger number of questions that have undergone extensive testing using qualitative and quantitative methods. Every PROMIS short form measure or CAT draws a select number of questions from the calibrated item bank to provide reliable and valid assessments of the HRQOL domain of interest. In short, PROMIS item banks offer the potential for efficient, flexible, and precise measurement of commonly studied dimensions of HRQOL. They are efficient because they minimize the number of items administered without compromising reliability, flexible because they allow the use of interchangeable items, and precise because they minimize the standard error of estimate [49]. Consequently, application of IRT

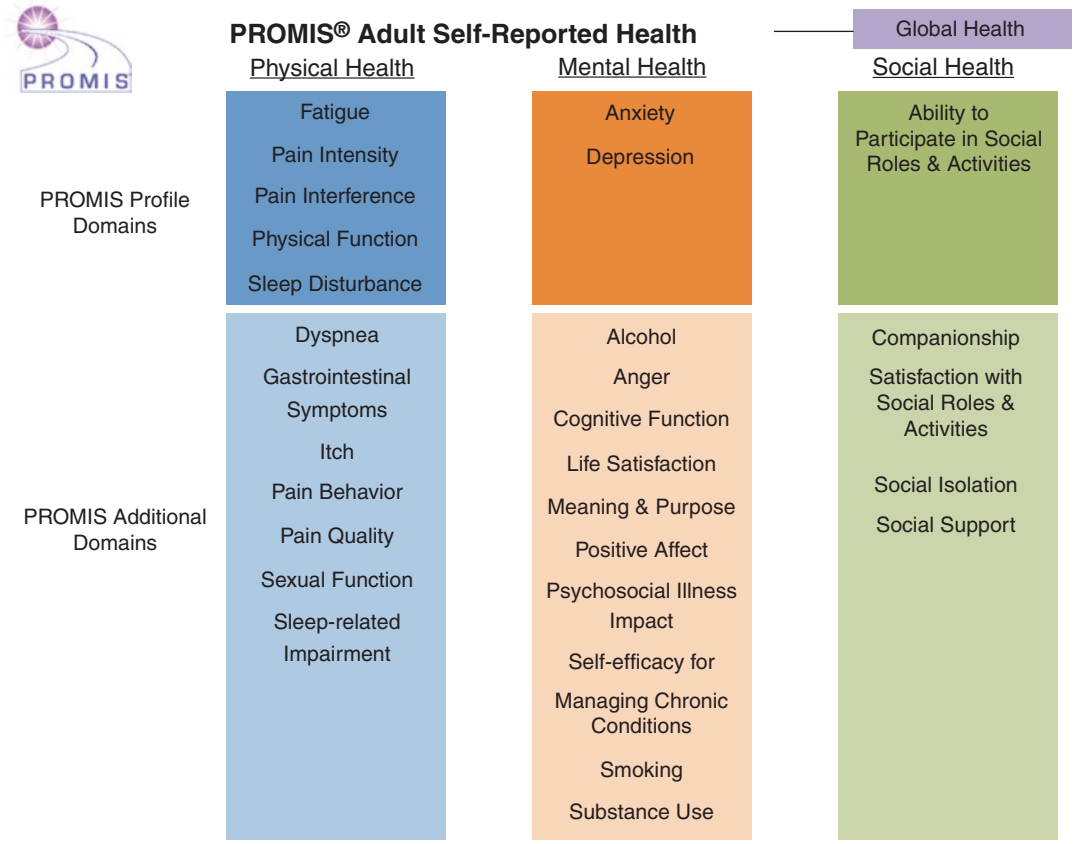

Fig. 24.1 The PROMIS Profile Domains Organized into the World Health Organization's Tripartite Model of Physical, Mental, and Social Health

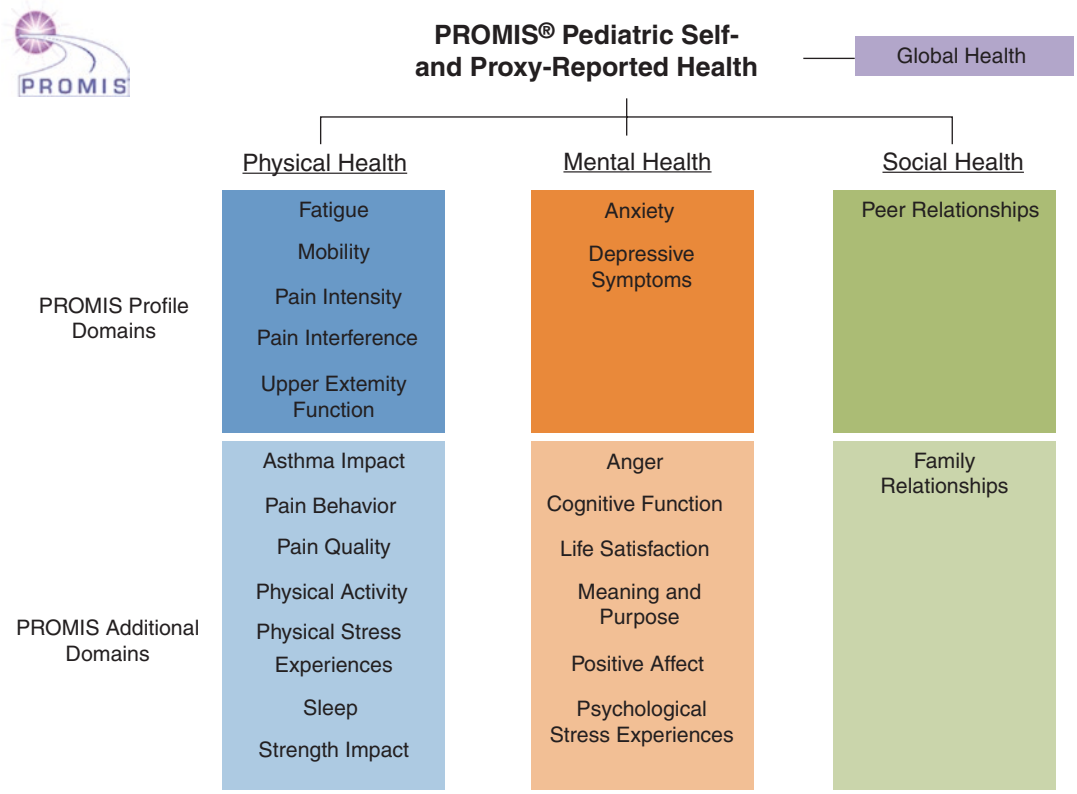

Fig. 24.1 (continued)

and CAT tools may allow for briefer assessments, more efficient assessments, and assessment of more symptoms and HRQOL domains of interest than has been typical in traditional assessments.

An added advantage of PROMIS is that scores are easily interpretable. Scoring is standardized so that the mean of all PROMIS measures is 50 and the standard deviation is 10. Higher scores represent more of the underlying construct. For example, higher depression scores may indicate more negative mood and negative cognitions, thus suggesting poorer mental well-being; whereas higher physical function scores may indicate a greater ability to successfully complete daily activities and household chores, thus reflecting better physical well-being. Available reference values include norms based on the U. S. general population, as well as clinical samples, such as patients with cancer. In addition, the initial PROMIS norming sample was large enough to estimate subgroup norms by gender and age range [50].

To inform the clinical utility of PROMIS measures, severity thresholds were identified for multiple measures. These "cut points" enable individual practitioners to assess patient response to interventions and modify treatment plans accordingly. PROMIS scientists created score graphs for PRO domains to enhance the meaningfulness of PROMIS scores (see Fig. 24.2). Drawing from the large-scale calibration testing data [49, 51], the percentage of participants that would fit into each category (0.5, 1.0, and 2.0 standard deviations) were reviewed. Then, through a process known as "Bookmarking," thresholds for severity levels (e.g., no problems, mild problems, moderate problems, severe problems) were established in several clinical samples [52]. Notably, severity

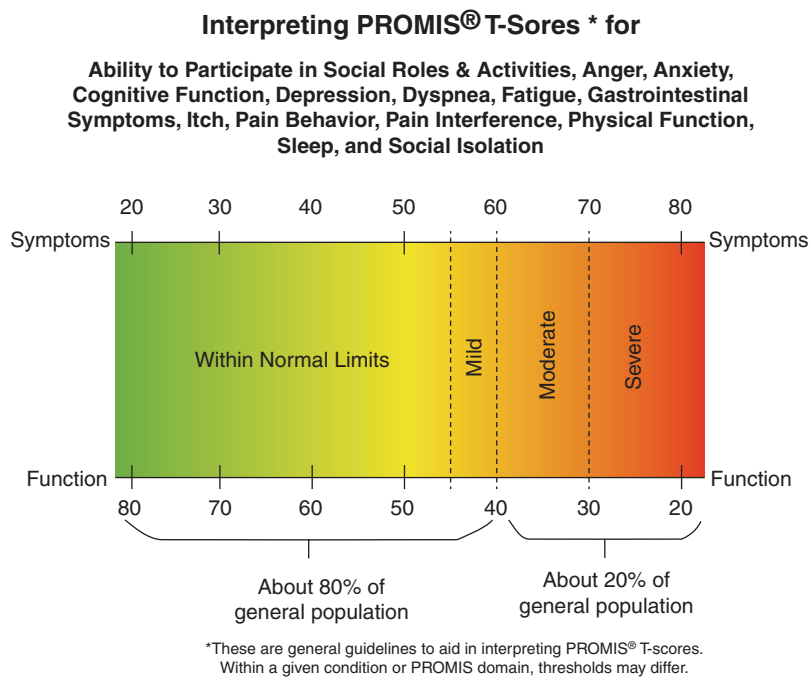

Fig. 24.2 An Example of a PROMIS Score Graph Created to Enhance the Meaningfulness of PROMIS Scores

thresholds in patients with cancer exist for PROMIS Pain Interference, Fatigue, Anxiety, Depression, Physical Function, Cognitive Function, and Sleep Disturbance [53, 54].

Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) From 2008 to 2014, the NCI and its contracted researchers developed PRO-CTCAE for use in cancer therapeutic trials and other cancer-related research in order to integrate the patient's voice and experience in describing toxicity, symptoms, and adverse events (AEs) from cancer treatment [55, 56]. PRO assessment in cancer therapeutic trials is important because it provides the patient's perspective on how a treatment is affecting their HRQOL, facilitates higher quality patient–provider communication on the trade-offs between survival benefit and treatment-related morbidities [57, 58], and PRO toxicity reporting may be more accurate than clinician ratings for certain symptoms [59, 60]. To develop PRO-CTCAE, researchers identified the AEs most amenable to patient self-report (e.g., subjective AEs like pain), created items to represent each AE domain and ensure it aligns with the CTCAE criteria, conducted qualitative and quantitative studies to evaluate and refine the PRO-CTCAE items, created software for the collection of PRO-CTCAE data, conducted usability testing of the PRO-CTCAE software, and established guidelines for implementation of PRO-CTCAE in cancer therapeutic trials (see Basch et al., 2014 [55] for a complete review of this process).

The multidisciplinary team had to ensure that a PRO version of the CTCAE reporting system was flexible enough to allow investigators to choose only the AEs most relevant to their specific trial (as opposed to a fixed list of symptoms/constructs as in most existing HRQOL measures), include AEs that occur infrequently (e.g., blurred vision) to very frequently (e.g., nausea), capture the worst magnitude of each AE, and assess the AEs at appropriate intervals. The final PRO-CTCAE standardized measurement system assesses 78 AEs using 124 items and allows clinicians and researchers to select the AEs most relevant to their trial.

All PRO-CTCAE items follow the same structure. They use a plain language term for the AE of

interest, include the attribute of interest (frequency, severity, interference with activities of daily living), and a recall period (typically the previous 7 days). The attributes assessed in each item were determined based on the attributes used in grading the corresponding CTCAE domain. For example, some CTCAE domains grade the AE based on both the frequency of the symptom and the severity of the symptom. In this example, the PRO-CTCAE domain would include one item assessing frequency (e.g., In this past 7 days, how often did you have [symptom]?) and a second item assessing severity (e.g., In the past 7 days, what was the severity of your [symptom] at its worst?). With the seven-day recall period, it is recommended that PRO-CTCAE items are answered on a weekly basis to ensure no AEs are missed. On average, it takes patients between 4 and 6 min to complete approximately 28 PRO-CTCAE items [61], thus minimizing participant burden in completing PRO items throughout the trial [55].

The validation studies of PRO-CTCAE found that all PRO-CTCAE items were correlated in the expected direction with validated HRQOL measures, and the majority of PRO-CTCAE items were higher in patients whose physicians scored their performance status as more impaired compared to patients with less impairment [62]. Additionally, most items had high test–retest reliability when assessed approximately 1–6 weeks apart, and the correlation between PRO–CTCAE item changes and the change in the corresponding HRQOL domain were statistically significant in most of the prespecified items [62]. PRO-CTCAE was originally developed for use in adult cancer patients and was translated to a few common languages (e.g., Spanish). Since 2014, the PRO-CTCAE has been translated into 31 languages and pediatric PRO-CTCAE items (both patient self-report and caregiver-report) have also been validated and are now available for use [63, 64]. To find the most up-to-date information on PRO-CTCAE, please see the NCI's website for PRO-CTCAE (https://healthcaredelivery.cancer.gov/pro-ctcae/).

Integration of PROs into Cancer Clinical Trials

The use of PROs to assess HRQOL among cancer patients and survivors has grown exponentially, as described above. With the growth in this area of research and the development of rigorous measures, the current scientific focus has shifted to the usefulness of PROs in a variety of settings, specifically cancer clinical trials and cancer care delivery. The shift toward including PROs in cancer clinical trials started after research documented that the inclusion of baseline HRQOL (assessed by PROs) in multivariable models improved survival and mortality predictions over and above clinical variables [65–70]. Population-based data suggests that baseline HRQOL is significantly associated with all-cause mortality [68], and data pooled across multiple clinical trials found that inclusion of baseline HRQOL improved prognostic accuracy by 5.9–8.3% [69]. Overall HRQOL, physical function, dyspnea, pain, and appetite loss appear to be the most predictive indicators of mortality/survival [65, 66]. Baseline HRQOL was also found to be a better predictor of survival than performance status [65]. In 21 of the 39 studies (54%), clinician-rated performance status was no longer a significant predictor of survival if at least one HRQOL PRO was included in multivariable models [67]. In addition to improved survival predictions, HRQOL data can also provide the patient's perspective on a treatment's impact on function and well-being, supplement efficacy and safety data, and facilitate higher-quality patient–provider communication on the balance between survival benefit and treatment-related morbidities when choosing a treatment option [57, 58]. Therefore, the inclusion of HRQOL PRO endpoints should become standard practice in trial design, especially in oncology where treatments often carry a

high side-effect burden with marginal improvements in survival benefits.

However, the inclusion of HRQOL PROs in clinical trials, their use in drug labeling claims, and their dissemination in the scientific literature are subpar [71]. Even among trials that have incorporated PROs as primary or secondary outcomes, complete reporting of the PROs rarely occurs. Among 794 randomized controlled trials, only half provided a rationale or hypothesis for the chosen PRO, a quarter included information on how missing data was handled, and slightly more than half actually described the results of the HRQOL PROs [72]. To ensure accurate reporting of PRO findings, to utilize PRO findings in drug labeling claims, and to disseminate PRO findings to clinicians for use in treatment discussions, specific guidelines on how to integrate HRQOL PROs have been developed by both researchers and regulatory agencies.

Professional Organization Guidelines and Recommendations Researchers and professional organizations focused on the study of PROs and HRQOL have developed PRO-specific extensions to the widely used Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) and Consolidated Standards of Reporting Trials (CONSORT) guidelines to assist researchers in integrating HRQOL endpoints into trial designs. Both the SPIRIT-PRO [73] and CONSORT PRO [74] extensions added PRO-specific expansions to existing items and added new items for trials that include HRQOL primary or important secondary outcomes. A complete, detailed overview of the guideline development process and the updated SPIRIT-PRO [73] and CONSORT PRO [74] checklists can be found elsewhere but are described briefly here.

Clinical trials including HRQOL as a primary outcome or an important secondary outcome should (1) provide a rationale for including PROs and why specific HRQOL domains were chosen; (2) state any HRQOL-specific objective and/or hypothesis; (3) describe which PRO measure will be used to assess each HRQOL dimension, and include measurement properties (e.g. reliability, validity), who is completing the PRO (e.g., patient or proxy), and data collection method (e.g., paper survey, telephone interview); and (4) identify the statistical methods used for analyzing each HRQOL outcome and approaches used to handle any missing data. Additionally, for trials that include HRQOL as a primary endpoint, sample size calculations should be described.

The SPIRIT-PRO guidelines recommend additional points specific to clinical trial protocols: (1) indicate the individual(s) responsible for any HRQOL PRO-related trial content; (2) describe any PRO-specific eligibility criteria that is different from eligibility criteria for the overall trial (e.g., language requirements), and, if applicable, provide the rationale for choosing to collect PROs from only a subsample; (3) outline the schedule of HRQOL PRO assessments, provide rationale for the chosen time points, describe the order of assessments (e.g., multiple questionnaires, PROs assessed at same visit as clinical indicators), and, if applicable, provide a justification for measuring baseline HRQOL prior to randomization; (4) indicate what metric will be used in analysis (e.g., change in HRQOL PRO from baseline); (5) list any strategies that will be employed to minimize missing data; and (6) outline how you will use PRO data for patient monitoring in a standardized manner, if applicable. In reporting the final results of a clinical trial, the CONSORT PRO guidelines also recommend that trials (1) identify the HRQOL domain as a primary or secondary outcome in the abstract; (2) outline any PRO-specific limitations or concerns of generalizability to larger population and/or clinical practice; and (3) interpret HRQOL findings in the context of the trial's clinical findings, if applicable. Finally, the CONSORT PRO guidelines emphasize the importance of publishing HRQOL findings with the primary publication even if this data is included as a supplement.

Regulatory Agencies Guidelines and Recommendations Regulatory bodies such as the FDA, the oncology-specific divisions of the FDA (e.g., Office of Hematology and Oncology Products, Oncology Center of Excellence), and the

European Medicines Agency (EMA) have developed their own recommendations and guidelines for integrating HRQOL PRO endpoints into clinical therapeutic trials in order to use the data to support drug labeling claims. These recommendations and guidelines include many of the points highlighted above. For example, the FDA's Office of Hematology and Oncology Products recommends that researchers select HRQOL PRO endpoints closely related to the disease and/or treatment under study, and they have identified symptomatic AEs, physical function, and disease-related symptoms as the key PROs for oncology drug labeling assessments [75]. The complete guidance documents from the FDA for the use of PRO endpoints in drug labeling claims and in medical device approvals, and the EMA's guidance for anticancer drug labeling claims can be found elsewhere [3, 58, 76], and we have summarized this guidance in Table 24.2.

PRO Endpoints in Oncology Drug Labeling Claims Despite the development of the SPIRIT-PRO and CONSORT PRO recommendations and the FDA's guidelines, few oncology drugs have FDA-approved PRO claims. From 2010 to 2014, the FDA's Office of Hematology and Oncology Products approved 40 oncology-focused products (25% of all submitted applications). Of the approved oncology drugs, only three (7.5%) received an HRQOL PRO claim [77], a figure substantially lower than seen across all drugs approved by the FDA in a similar time period (16.5%) [78]. Among oncology drugs approved by both the FDA and the EMA between 2012 and 2016, 70.3% of the applications included HRQOL PRO data, but no FDA-approved products included PRO labeling [79]. In contrast, the EMA included HRQOL PRO-focused claims in 46.7% of their oncology product labeling [79]. The reasons for this discrepancy include the EMA's higher likelihood of accepting legacy PRO instruments, like the EORTC and the FACT measures for PRO-specific product labeling, and the nature of oncology trials [77, 79]. Oncology trials are often fast-tracked, and this shorter time frame precludes the ability of the investigative team to develop a PRO measure that conforms to FDA's standards. Additionally, the FDA has typically not approved a PRO-based claim unless the trial is double-blinded, and oncology trials are most often conducted as open-label trials. Despite a recognition by the FDA that

Table 24.2 Guidelines for Integrating HRQOL PROs into Clinical Trials

Recommendation	FDA	EMA
Rationale for inclusion of PRO measure	X	X
List PRO-specific study objectives and hypotheses	X	X
Provide PRO instrument details		
The instrument's conceptual framework	X	
Copy of instrument (including previous versions)	X	
Instructions/user manuals	X	
Data collection method (e.g., electronic, patient-administered, etc.)	X	X
Documentation of instrument's psychometric properties (e.g., reliability, validity), including complete results of all studies done to ensure validity (e.g. cognitive interview transcripts)	X	X
Demonstrate validity/reliability in the same population being studied in trial	X	X
Any modifications made to the instrument, rationale for modification, the process for making the modification, and data supporting that all psychometric properties were maintained	X	X
Scoring algorithm	X	X
Describe targeted labeling claim(s), disease/condition, and population of focus	X	
Describe how scores are interpreted to be clinically meaningful	X	
Provide methodological details		
Timing of PRO assessments	X	X
Trial duration and demonstrate that it provides enough time to assess PRO endpoints	X	X
Plans for missing data	X	X
Statistical analysis plan, including power/sample size calculations	X	X
Plans for clinical management of adverse events assessed via PRO measures		X
Follow the CONSORT PRO checklist		X

Note: FDA Food and Drug Administration, *EMA* European Medicines Agency

these characteristics of oncology trials are present, there has not be substantial progress or collaboration between the FDA, industry, clinicians, and PRO researchers to identify alternative solutions [80].

Importance of the Patient Voice HRQOL data provide important information about treatment side effects and this data play a central role in patient–provider discussions about treatment options. Given the lack of inclusion of HRQOL PRO data in oncology drug labeling claims, the FDA's Oncology Center of Excellence has tried to make progress in improving patient and clinician access to HRQOL data from therapeutic trials by creating Project Patient Voice. Project Patient Voice is an online platform for cancer patients, their caregivers, and clinicians to look at patient-reported symptom data from the therapeutic trials of approved anticancer treatments [81]. Project Patient Voice is currently in its pilot phase and is displaying the HRQOL data collected during the first six months of one drug trial. Visitors to the website can click on individual symptoms to see graphical depictions of the data. If Project Patient Voice is found to be a usable and informative website for cancer patients, their caregivers, and clinicians, the FDA's Oncology Center of Excellence has plans to include results from other trials.

Within the context of therapeutic trials, the patient voice is particularly meaningful for better understanding the adverse events or unexpected medical problems that occur during treatment. Adverse events have traditionally been assessed through clinician ratings of the CTCAE. However, data from cancer therapeutic trials suggest substantial disagreement between patient- and clinician-ratings, and likely under-reporting of toxicities/symptoms by clinicians [59, 60]. A pooled analysis of more than 1000 patients who participated in cancer therapeutic trials found that agreement between clinicians and patients (measured by Cohen's k) was low, ranging from 0.15 to 0.45 [60]. Di Maio et al. (2015) also found that clinicians likely under-reported 40.7–74.4% of toxicities reported by patients.

Clearly, improving both clinician and patient assessments of HRQOL domains, adverse events, and symptoms is important. HRQOL's ability to predict survival is improved when both clinician- and patient-ratings are included in multivariable models [69]. Research among 1636 patients enrolled in therapeutic trials found that the disagreement between clinician- and patient-ratings of performance status and nutrition was a significant predictor of mortality [82]. This discrepancy between patient and clinician perceptions and the resulting implications for care were primary catalysts for the development of the PRO-CTCAE as described above.

Next Steps in Improving HRQOL Integration in Clinical Trials The use of HRQOL PRO endpoints in clinical trials, both therapeutic and supportive care trials, provides opportunities to include the patient's voice, understand treatment side effects, make informed decisions on the best available treatments for cancer, and identify potential interventions to improve HRQOL. Important governmental and regulatory bodies (e.g., FDA, EMA) have recognized the value of HRQOL PRO endpoints in developing, testing, and licensing cancer-specific drugs and medical devices. However, the inclusion of PRO endpoints in cancer clinical trials continues to be low, and work continues to fully integrate PROs into cancer therapeutic trials in a rigorous manner. Efforts by the NIH and the NCI to develop high-quality PRO measures for HRQOL, symptoms, functioning (PROMIS), and AEs (PRO-CTCAE) may begin to overcome barriers to PRO-based inclusion in cancer clinical trials.

Integration of HRQOL PROs in Cancer Care Delivery

With both the knowledge that assessment of HRQOL, symptoms, and treatment toxicity provide valuable information and the development of robust PRO measures (e.g., PROMIS, PRO-CTCAE), researchers and organizations have

begun to consider the utility of integrating PRO measures into cancer care delivery. Eliciting the patient's voice during cancer treatment and survivorship has been shown to improve patient–provider communication, patient satisfaction, patient engagement, and HRQOL [83–86]. More recent studies of symptom tracking (using PROs) has demonstrated reduced emergency department visits, treatment-tailoring, increased tolerability to cancer treatment for longer intervals, and subsequent improvements in survival [87–91]. The integration of HRQOL PROs into cancer care has the potential to improve the quality of care delivery through the early identification of problems, improvements in symptom management, and triaging care based on needs (e.g., referrals and in-person intervention for severe symptoms, self-management for moderate symptoms) [83]. For healthcare organizations to achieve these goals, however, the integration of PROs must be evidence-based, aligned with their specified objectives, and follow implementation guidelines.

Evidence-Based Approaches to HRQOL Monitoring Researchers have identified feasible and acceptable approaches for monitoring changes in HRQOL among cancer patients. The most frequently studied methods for integrating HRQOL PROs into cancer care delivery are clinic-based assessments and home-based reporting using patients' own digital devices.

Options for clinic-based assessments of HRQOL PROs include paper-based surveys and tablet/touch-screen computers provided to patients in waiting rooms. Pilot studies of clinic-based assessments have demonstrated participation rates ranging from 59–90% [84, 92–98], reasonable retention rates (61–84% of study participants completing assessments throughout study period) [93–95, 97], and high patient and clinician satisfaction across samples diverse in age, gender, cancer type, disease stage, and treatment exposure [93, 99, 100]. Pilot studies have also found data equivalence across paper-based or electronic-based surveys completed in clinics with results suggesting lower levels of missing data for electronic collection [98, 99, 101–103].

The second method for HRQOL PRO assessment, home-based reporting, includes web-based portals patients' access from a home computer, telephone-assisted interviews, and smartphone apps. Across these different approaches, pilot studies found highly variable participation rates (35–86%) [70, 86, 104–113], but reasonable retention (58–91%) [70, 104, 106, 107, 114] and completion rates (most studies reporting 60% completion or above [104, 106, 107, 110, 112, 114–117], with some exceptions) [111, 118]. Systems that actively alerted/reminded patients to complete PRO assessments appear to have better participation rates. A pilot randomized controlled trial of a web-based app developed to improve medication adherence in breast cancer survivors found significantly higher completion rates in the group who received reminders (74%) compared to the group who did not receive reminders (38%) [119].

Patients were satisfied with these systems and found the electronic systems easy to navigate; this was true even for patients with lower technology literacy [92, 97, 104, 106, 107, 120–124]. In particular, patients liked home-based, self-monitoring because they felt more knowledgeable about their health, were able to self-manage, and were reassured that their healthcare team was monitoring their symptoms and functioning to ensure timely response to problematic trends [86, 88, 97, 115]. Both clinic-based and home-based approaches to HRQOL PRO assessments are feasible and acceptable approaches for cancer patients, and the numerous options available allow organizations to choose a mode of PRO collection that is tailored to their local resources and patient population.

Monitoring HRQOL PROs alone does not appear to be enough to make significant improvements in the outcomes important to cancer patients [94, 125]. PRO monitoring may increase the frequency of HRQOL discussions during clinic appointments, but data suggest that HRQOL and/or symptom distress improve only if PRO data summaries are provided to clinicians with clinically actionable information [94, 125].

For example, Ruland et al. (2010) provided clinicians a summary of the HRQOL and symptom domains patients had ranked as the most in need of management or attention, and they found significant reductions in symptom distress in the patients whose summaries were provided to their clinicians compared to patients whose summaries were not provided to clinicians. In contrast, Hilarius et al. (2008) provided nurses with a graphical summary of patients' responses to EORTC QLQ-C30 but provided no further information on how to utilize this information. When comparing the HRQOL of these patients to those who did not have a summary provided to their nurse, the authors found no significant difference in HRQOL. However, monitoring HRQOL does improve patient satisfaction and patient–provider communication [93, 121, 122].

PRO monitoring interventions that include one or more of clinician alerts, tailored self-management information, referrals, or clinical decision support (e.g., specific management recommendations) have been found to significantly improve HRQOL domains, including symptom burden and symptom distress [95, 109]. In a randomized controlled trial that assigned cancer patients to one of three distress screening groups (minimal screening [Distress Thermometer only], full screening + personalized summary, and triage (full distress screening and phone triage for referrals), receipt of a referral was the best predictor for changes in anxiety and depression [126]. A large-scale randomized controlled trial of cancer patients receiving chemotherapy (N = 766) randomized patients to clinic-based symptom monitoring (intervention group) or standard of care symptom monitoring (control group) [84]. In addition to completing the symptom assessments, intervention group participants also had their results summarized, provided to nursing staff, and nurses were immediately alerted when any symptom reached the severe threshold. Patients in the intervention group had significantly higher HRQOL, were less likely to be admitted to the emergency room, and remained on chemotherapy longer than patients in the control group. Similar patterns have also been found in studies examining home-based monitoring that delivers tailored symptom self-management information directly to the patient [127].

Systematic Approach to PRO Integration Regular HRQOL PRO assessments will only lead to improved outcomes if implementation is done in a systematic and rigorous manner.

Table 24.3 Integrating HRQOL PROs into Cancer Care Delivery

Recommendation	Examples
Identify goal of HRQOL PRO data collection	One-time screening tools (e.g. distress screening) Regular symptom monitoring (e.g. early identification of treatment toxicity)
Determine population of focus for HRQOL PRO collection	Disease or treatment Phase of the care continuum Minority group (age, race/ethnicity, rurality, sex/gender)
Identify the specific HRQOL domains to target	Physical domain Mental domain Social domain Spiritual domain
Determine timing of HRQOL PRO assessments	Post-discharge for cancer-related surgery [105, 112] Link assessments with clinic visits [117, 227] Specified intervals in posttreatment survivorship [118]
Choose the PRO instrument	Generic Cancer-specific Disease-specific Symptom or treatment-specific
Select mode of PRO administration	Paper (either in clinic or mailed to patients' homes) Electronic (using tablets/laptops in clinic or mobile/web-based on patients' devices) Telephone (by clinic staff or through automated services)
Identify who will receive HRQOL PRO results	Clinicians Patients Caregivers
Select format for PRO results presentation	One-page summaries Summary dashboards Graphical interpretations [228, 229]
Provide guidance on PRO score interpretation	Clinical thresholds for action Clinical decision support recommendations [96]

Researchers and professional organizations have outlined methodological and implementation considerations for the integration of HRQOL PRO assessment in clinical care [128], and we have summarized these recommendations in Table 24.3. The implementation of HRQOL PRO assessment and how PRO results are used will vary if organizations want to use PROs as one-time screening tools (e.g., distress screening) or for regular symptom and AE monitoring (e.g., early identification of treatment toxicity). Additionally, the PROs selected for assessment need to be relevant to the target patient population and amenable to intervention [129–131].

When selecting HRQOL PRO measures, organizations should choose measures that are validated for use in the target population, ideally in the same mode the questionnaire will be administered in clinical practice, and are easy to implement [132]. Tailoring the mode of administration to patient preferences (e.g., paper- or telephone-based in older populations) will likely improve participation rates. The primary modes of PRO questionnaire administration (paper, web-based, phone) have had high response rates in prior literature [84, 104, 106, 107, 110, 115, 116]. Additionally, a number of publications have found similar completion times and data equivalence when the same measures are implemented in paper or electronic forms [98, 99, 101–103]. A meta-analysis of data equivalence in 278 scales found that the average mean difference between paper- and electronic-based surveys was 0.2% and the average weighted correlation between modes was 0.90, further supporting the recommendation to select a method tailored to patient preferences [133].

Clinicians prefer easy-to-interpret, digestible reports of PRO data (e.g., one-page summaries, summary dashboards with options for additional detail) that clearly highlight clinical thresholds for action [116, 134–136]. Patients like having summaries of their HRQOL results, but it is most important to them that their clinical team is tracking their HRQOL PRO results and using them in their care [110]. Identifying thresholds for meaningful PRO results can be done through both psychometric and consensus-building approaches. Psychometric options for score interpretation include using minimally important differences, comparisons to normative data, reference values, and benchmarks to identify meaningful change and/or severity thresholds across multiple HRQOL domains (e.g., symptoms, function, distress) [137–140]. Ideally, when selecting a PRO measure, it is preferable to find one with psychometrically derived severity thresholds in the population of interest. When this information is not available, organizations have used consensus-building approaches to identify thresholds (e.g., the bookmarking approach described above for PROMIS) [52, 141]. Regardless of the selected approach, organizations should regularly evaluate and modify these thresholds, as needed, to ensure that patients are receiving intervention at the appropriate time and level, when needed [83].

The results from HRQOL PRO assessments can be used in clinical care through two primary avenues: self-management resources delivered directly to patients and clinical alerts delivered to clinicians (with or without specific recommendations for management). Most often, organizations identify thresholds that categorize patients into four groups (no, mild, moderate, and severe symptoms/concerns), and clinical actions are tailored to increase clinical staff engagement with increasing severity [112]. For interventions that focus on home PRO monitoring, the most common approach is to deliver self-management information directly to patients in the mild/moderate categories and send alerts directly to clinical staff for patients in the severe category [97, 105, 112, 122, 142]. In some cases, patients in the moderate category will be told to contact their clinic team during business hours, and patients in the severe category will be told to go to the emergency room [143]. Regardless of which groups receive self-management information, patients prefer personalized and tailored self-management information [88, 105, 113, 142]. For interventions that focus on clinic-based PRO assessments, results are summarized and provided to clinicians, and in many cases, these summaries are

coded to highlight scores that have reached different thresholds (e.g., moderate, severe), and clinical decision support recommendations are provided [96]. Clinical recommendations that are short, include both pharmacological and non-pharmacological management approaches, and are tailored to local resources are more likely to be implemented into clinic workflow and be rated more positively by clinicians [129, 130, 144].

HRQOL in Care Delivery The integration of HRQOL PROs into cancer care delivery has become more widespread and sophisticated across time, and the value of collecting HRQOL outcomes is well-accepted [145]. Regular assessment has been found to improve the timely identification of symptoms, referrals for psychosocial services, and patient–provider communication [83]. To ensure positive patient outcomes from HRQOL PRO assessments, organizations need to consider important implementation topics such as identifying the most appropriate HRQOL domains, measures, and clinical response options. Guidelines from professional organizations [128] and published papers [142, 146] describing the development of PRO systems can serve as useful starting points for institutions interested in integrating HRQOL assessment into cancer care.

Summary and Future Directions

HRQOL is a multidimensional concept that includes self-reported symptoms, functional abilities, and physical, mental, social, and spiritual health perceptions. HRQOL is measured with a variety of valid PROs. Global and specific approaches to assessing HRQOL may permit comparisons to healthy populations and within particular disease groups, respectively. Efforts to enhance and improve PROs that assess HRQOL are ongoing with initiatives such as PROMIS and PRO-CTCAE providing valid, brief, and flexible measurement approaches for patients with cancer and survivors. HRQOL is increasingly an important but underutilized PRO in cancer clinical trials and care delivery research. To further catalyze HRQOL research and maximize cancer clinical care, future research should incorporate a multilevel approach that accounts for patient (e.g., identifying HRQOL priorities across the care continuum, empowering decision-making and self-management), provider (e.g., minimizing workflow interruptions, making PROs actionable), and system (e.g., integrating PROs into the electronic medical record, harnessing technology as a rapid learning healthcare system) level perspectives. Optimizing patient-centered care, enhancing HRQOL, and attaining better outcomes are aspirational and achievable goals.

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