Angelos P. Kassianos *Editor*

Handbook of Quality of Life in Cancer

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This work is dedicated to Panayiotis Kassianos (1945–2006).

Preface

Is quality of life more important or is it quantity of life? Or is it up to the patient to decide? The evidence on the importance of quality of life (QoL) for patients, their lives and their treatment has been widely documented in the literature. There is considerable research on the role of QoL on general well-being, responsiveness to treatment and even longevity. Therefore, it is possible that QoL can even impact quantity of life. At the same time, there are a number of methodological considerations when measuring and assessing QoL with cancer patients. This handbook aims to fill a gap in the literature, collate evidence and bring world experts together to respond to a number of questions, among others, including:

1. What is QoL, why it is important and how is it assessed?
2. What are the theoretical and methodological considerations in assessing QoL with cancer patients?
3. How can QoL be utilised in routine clinical care?
4. How is QoL impacting different cancer populations in terms of site, age, gender and context?

The Handbook of Quality of Life in Cancer summarises current evidence and can be useful for a diverse readership. First, researchers who wish to use QoL assessment tools in clinical trials or other types of research studies. Second, healthcare practitioners including clinicians, nursing professionals, social workers, physiotherapists and psychologists, among others, who want to develop their understanding of how they can utilise QoL in their practice and its importance for the patients they care for. Third, commissioners who can understand why QoL may impact population health and the implications for costs of healthcare systems. Fourth, teachers and academics who can use the handbook to inform their teaching and prepare materials, exam questions or essay topics and facilitate debates in their teaching. Finally, students in diverse fields of study including medicine, nursing, psychology, social work, medical sociology, population health, epidemiology, medical statistics and others who can use the handbook for their studies and for their continuing professional development.

You can use this handbook in different ways that fit your learning purpose. We tried to summarise evidence in each chapter and provide elements that can help you to check your understanding of each topic and facilitate discussions with others either in a classroom or in practice. These elements include:

1. *Questions that can be used in teaching and to test learning*. These are questions that the authors of each chapter have considered carefully in order to help you to test and summarise your knowledge on each topic.
2. *A topic that can be used for discussion in teaching.* These topics are considered key for each chapter and can help facilitate debates and classroom interactive discussions as well as help you to consider issues that can be controversial or that can help develop your critical thinking on the topic.
3. *A 'further reading' list.* These lists are different than the reference lists for each chapter. The purpose here is to highlight what are the important publications for each topic so that you can easily expand your knowledge and identify further resources.
4. *A 'research in context' box* where authors have identified a key topic, publication or tool and have expanded on this with more details so that you can get further in-depth knowledge of a topic.

The first part of the handbook, *Concepts and Definitions*, is introductory and here you can read about important concepts and definitions. Concepts like QoL, health-related quality of life (HRQoL) and wellbeing are defined in Chap. 1, while Chap. 2 deals with what it means for patients to have QoL in relation to quantity of life.

The second part of the handbook, *Quality of Life Assessment*, deals with different aspects of assessing QoL of cancer patients. Generic tools like the WHOQOL group of tools are discussed in Chap. 3, while cancer-specific tools developed by the European Organisation for Research and Treatment of Cancer (EORTC) and the Functional Assessment of Chronic Illness Therapy (FACIT) measurement systems are discussed in detail in Chaps. 5 and 6, respectively. Chapter 4 outlines all aspects that should be considered when developing a cancer QoL assessment tool, and Chap. 7 outlines what should be considered when validating the tools. Modern technologies in assessing QoL are becoming more prevalent and will continue to be in the years to come. These are discussed in terms of using new technologies for QoL assessment in Chap. 8 and in terms of modern psychometric measurement and computerised adaptive testing in Chap. 9.

The third part of the handbook, *Best-Practice Elements When Assessing Quality of Life*, deals with best-practice elements of using QoL data. How the data can be analysed in clinical trials and beyond is discussed in Chap. 10, and how data can be presented visually to communicate these to patients and clinicians is discussed in Chap. 11. Subsequently, Chap. 12 outlines cross-cultural considerations of QoL assessment such as cultural validity and considerations when translating measures or using them with diverse populations and contexts. A number of subsequent chapters outline which topics QoL data can be used for and inform such as mortality aspects (Chap. 13), healthcare cost-effectiveness (Chap. 14), patient satisfaction with care in the context of patient-reported experience measures (Chap. 15), decision-making in health care (Chap. 20) and drug development (Chap. 21). Chapter 16 focuses on a specific symptom (fatigue) that warrants greater focus from researchers and clinicians, and Chaps. 17 and 18, respectively, outline the use of QoL data for specific populations (adolescents and young adults) and as a proxy

measure for patients. Chapter 19 outlines the evidence on studies with psychosocial interventions with QoL as an outcome and how mental health can be related to QoL.

The fourth part of the handbook, *Case Studies of Using Quality of Life Tools for Specific Cancer Types*, presents some case studies on QoL aspects of specific cancer populations: breast cancer (Chap. 22), brain cancer (Chap. 23), colorectal cancer (Chap. 24), endometrial cancer (Chap. 25) and melanoma (Chap. 26). These chapters offer more in-depth information on patients with different tumour sites and how their QoL can be affected, as well as the specific tools that can be used for these populations.

The Handbook of Quality of Life in Cancer makes a unique contribution to knowledge by collating contemporary evidence and perspectives with practical guidance. It is also designed to be useful for a diverse readership and offers food for thought for new directions for research and clinical practice towards improving QoL for cancer patients.

London, UK Angelos P. Kassianos

Contents

About the Contributors

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Amélie Anota, PhD is a senior statistician at the Cancer Care Center Léon Bérard in France. She is expert in the longitudinal analysis of quality of life data in oncology. After obtaining a PhD in biostatistics in 2014 at the University of Franche-Comté, France, she realised a one-year research fellowship in the Health Outcomes Research Unit of the GIMEMA Fondazione in Rome, Italy. She previously worked at the University Hospital of Besançon and is also statistician for the French National Platform of Quality of Life and Cancer.

Iris Bartula, DCP is a clinical and research psychologist. She is a senior lecturer at the University of Sydney and leads supportive care and survivorship research at Melanoma Institute Australia. Both her clinical work and research efforts focus on improving quality of life and emotional wellbeing of melanoma patients. She has particular interest in the development, validation and implementation of psychometric measurements and psychosocial interventions. She is a strong advocate for consideration and integration of psychosocial support into a routine medical practice.

Melanie Bell, PhD, MS is professor in the Department of Epidemiology and Biostatistics at the Mel and Enid Zuckerman College of Public Health at the University of Arizona. Her research focus is statistical methods for handling missing data in randomised trials, and the design and analysis of studies using patient-reported outcomes. She has published extensively both in methodological issues in the design and analysis of patient-reported outcomes, as well as collaboratively for trials that use patient-reported outcomes.

Anne Brédart, PhD is a clinical psychologist and researcher in psycho-oncology at Institut Curie in Paris, France. She is an active member of the European Organisation for Research and Treatment of Cancer Quality of Life Study Group (EORTC QLG), where she implemented the development and validation of cancer patient satisfaction with care measures. She pursues clinical studies in the field of supportive care needs and quality of life assessment. She also coordinates a research program on psychological and communication issues in breast cancer genetics and advanced cancer care.

Jason Bredle, MFA is the director of licensing operations for FACIT.org and coordinates the translation and linguistic validation of the FACIT measurement system with FACITtrans in the United States. His contributions to linguistics and health outcomes have appeared in *Quality of Life Research*, *International Journal of Infectious Diseases*, *Journal of Palliative Medicine*, *Value in Health Regional Issues*, and *Pulmonary Therapy*, and have been presented at international forums in the United States, Canada, France and the Netherlands, among other places.

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Mbathio Dieng, PhD is a recognised expert in health economics, epidemiology and cancer quality of life research. She is currently a postdoctoral research fellow at the NHMRC Clinical Trials Centre, a specialised centre of the University of Sydney that has more than 25 years of expertise conducting randomised trials including landmark studies in cancer. Dr. Dieng has strong experience in within-trial and modelled economic evaluation applied to cancer, and her current research interests cover the areas of diagnostic tests, quality of life, benefits and harms of patient follow-up and monitoring, randomised control trials incorporating patient preferences, and the specific economic methods underpinning these.

Linda Dirven, PhD is an epidemiologist at the Leiden University Medical Center and Haaglanden Medical Center in the Netherlands. She became the chair of the EORTC Brain Tumour Group Quality of Life Committee in 2018. She is currently associate editor of *Neuro-Oncology*. The main focus of her research is clinical outcome measures in neuro-oncology, such as health-related quality of life, functioning in daily life, neurocognition, epilepsy and end-of-life care.

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Abbreviations

ACT	Acceptance and Commitment Therapy
ADL	Activities of Daily Living
AJCC	American Joint Committee on Cancer
ALL	Acute Lymphoblastic Leukaemia
ANOVA	Analysis of Variance
AQOL	Assessment of Quality of Life
AS	Active Surveillance
ATA	American Telemedicine Association
AUC	Area Under the Curve
AYAs	Adolescents and Young Adults
BCT	Breast-Conserving Therapy
BLA	Biological License Application
BP	Brief Psychotherapy
CAHPS	Consumer Assessment of Healthcare Providers and Systems
CAM	Complementary and Alternative Medicine
CASC	Comprehensive Assessment of Satisfaction with Care
CAT	Computerised Adaptive Testing
CAYA-T	Cancer Assessment for Young Adults-Testicular
CBT	Cognitive Behavioural Therapy
CCA	Cross-Cultural Adaptation
CDC	Centers for Disease Control and Prevention
CDF	Cumulative Distribution Function
CFA	Confirmatory Factor Analysis
CFI	Comparative Fit Index
CIs	Confidence Intervals
ClinROs	Clinician-Reported Outcomes
CNS	Central Nervous System
COAs	Clinical Outcome Assessments
COC	Consensus on Cancer
COS	Core Outcome Sets
COSMIN	COnsensus-based Standards for the selection of health Measurement INstruments
CRC	Colorectal Cancer
CRCI	Cancer-Related Cognitive Impairment
CrF	Cancer-Related Fatigue
CT	Chemotherapy / Cognitive Therapy / Computed Tomography

CUA	Cost-Utility Analysis
DFS	Disease-Free Survival
DIF	Differential Item Functioning
EC	Endometrial Cancer
eCDF	Empirical Cumulative Distribution Function
ECOG	Eastern Cooperative Oncology Group
EFA	Exploratory Factor Analysis
EHR	Electronic Health Records
EMA	European Medicines Agency
EORTC CAT	European Organisation for Research and Treatment of Cancer Computerised Adaptive Testing
EORTC QLQ	European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
EORTC QOL	European Organisation for Research and Treatment of Cancer Quality of Life
EORTC	European Organisation for Research and Treatment of Cancer
EPIC	Expanded Prostate Cancer Index Composite
ePROs	Electronic Patient-Reported Outcomes
ES	Effect Size
ESMO	European Society for Medical Oncology
FACIT	Functional Assessment of Chronic Illness Therapy
FACIT-SP	Functional Assessment of Chronic Illness Therapy-Spiritual Wellbeing
FACT	Functional Assessment of Cancer Therapy
FACT-Cog	Functional Assessment of Cancer Therapy-Cognitive Function
FACT-G	Functional Assessment of Cancer Therapy-General
FACT-GP	Functional Assessment of Cancer Therapy-General Population
FACT-M	Functional Assessment of Cancer Therapy-Melanoma
FACT-PWB	Functional Assessment of Cancer Therapy-Physical Wellbeing
FCR	Fear of Cancer Recurrence
FDA	Food and Drug Administration
FIGO	International Federation of Gynaecology and Obstetrics
FKSI	FACT Kidney Symptom Index
FLIC	Functional Living Index-Cancer
FPQLI	Ferrans & Powers Quality of Life Index
GDI	Good Death Inventory
GDP	Gross Domestic Product
GEE	Generalised Estimating Equation
HADS	Hospital Anxiety and Depression Scale
HBM	Health Belief Model
HCC	Hepatocellular Carcinoma
HCPs	Healthcare Professionals (or Providers)
HL	Hodgkin Lymphoma
HNPCC	Hereditary Nonpolyposis Colorectal Cancer

HPA	Hypothalamic Pituitary Adrenal (axis)
HRQoL	Health-Related Quality of Life
HRSA	Health Resources and Services Administration
HS	Perceived Health Status
HSCT	Hematopoietic Stem Cell Transplantation
HUI	Health Utility Index
IARC	International Agency for Research on Cancer
ICC	Intraclass Correlation Coefficient
ICD-11	International Statistical Classification of Diseases and Related Health Problems
ICER	Incremental Cost Effectiveness Ratio
ICI	Isolated Limb Infusion
ILP	Isolated Limb Perfusion
IOM	Institute of Medicine
IPOS	Integrated Palliative Care Outcome Scale
IPSS	International Prognostic Scoring System
IRT	Item Response Theory
ISOQOL	International Society for Quality of Life Research
ISPOR	International Society for Health Economics and Outcomes Research
IVR	Interactive Voice Response
JLA	James Lind Alliance
KPS	Karnofsky Performance Status
LAF	Lance Armstrong Foundation
LAYA-SRQL	Late Adolescence and Young Adulthood Survivorship-Related Quality of Life measure
LCI	Likely Change Index
LD	Local Dependence
LND	Lymph Node Dissection
LOA	Limits of Agreement
LoL	Longevity of Life
LS	Least Squares
MAR	Missing At Random
MAUCa	Multi-Attribute Utility in Cancer
MAUIs	Multi-Attribute Utility Instruments
MBCT	Mindfulness-Based Cognitive Therapy
MBSR	Mindfulness-Based Stress Reduction
MCAR	Missing Completely at Random
MCS	Mental Component Summary score
MCT	Meaningful Change Thresholds
MDASI	MD Anderson Symptom Inventory
MEK	Mitogen-activated protein kinase
MI	Multiple Imputation
MIDs	Minimal Important Difference
MMRMs	Mixed Models for Repeated Measures
MNAR	Missing Not at Random
MQOL	McGill Quality of Life
MSAS	Memorial Symptom Assessment Scale

MTC	Mastectomy
NATs	Negative Automatic Thoughts
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
NHL	Non-Hodgkin Lymphoma
NHS	National Health Service
NHSS	National Health Services Survey
NICE	National Institute for Health and Care Excellence
NIH	National Institutes of Health
NIS	National Insurance Services
NPC	Nasopharyngeal Carcinoma
ObsROs	Observer-Reported Outcomes
OECD	Organisation for Economic Co-operation and Development
ORR	Overall Response Rate
PASS	Power Analysis and Sample Size
PC	Prostate Cancer
PCM	Partial Credit Model
PCOC	Palliative Care Outcomes Collaboration
PediQUEST	Pediatric Quality of Life and Evaluation of Symptoms Technology
Peds FACT-Br	Pediatric Functional Assessment of Cancer Therapy – Brain
PedsQL	Pediatric Quality of Life Inventory
PerfOS	Performance Outcomes
PET	Positron Emission Tomography
PFS	Progression-Free Survival
PGIC	Patient Global Impression of Change
PhD	Doctorate of Philosophy
PHQ	Patient Health Questionnaire
PMH/PSQ	Princess Margaret Hospital Patient Satisfaction Questionnaire
PREMs	Patient-Reported Experience Measures
PRO-CTCAE	Patient-Reported Outcome – Common Terminology Criteria for Adverse Events
PROMIS	Patient-Reported Outcome Measures Information System
PROMs	Patient-Reported Outcome Measures
PRO-PMs	Patient-Reported Outcomes – Performance Measures
PROs	Patient-Reported Outcomes
PROTEUS	Patient-Reported Outcome Tools: Engaging Users and Stakeholders
QALY	Quality-Adjusted Life Years
QLG	Quality of Life Group
QLIC-ON	Quality of Life in Childhood Oncology
QLU-CIOD	Quality of Life Utility Measure-Core 10 Dimensions
QODD	Quality of Death and Dying
QOF	Quality and Outcomes Framework
QoL	Quality of Life
QOLCC	Quality of Life in Childhood Cancer

QOLIE	Quality of Life in Epilepsy Inventory
RCI	Reliable Change Index
RCT	Randomised Controlled Trial
REML	Restricted Maximum Likelihood
RI	Radiation-Induced Brain Injury
RIME	Relaxation, Mental Images and Spirituality
RMSEA	Root Mean Square Error of Approximation
ROC	Receiver Operating Characteristic Curve
RP	Radical Prostatectomy
RPM	Remote Patient Monitoring
RSM	Rating Scale Model
RT	Radiotherapy
RWD	Real World Data
RWE	Real World Evidence
SDC	Smallest Detectable Change
SEER	Surveillance, Epidemiology and End Results
SEM	Standard Error of Measurement
SES	Standardised Effect Size
SET	Supportive-Expressive Group Therapy
SF-12	Short Form 12
SF-36	Short Form 36
SG	Sun Ginseng
SGO	Society of Gynecologic Oncology
SISAQOL	Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints
SLNB	Sentinel Lymph Node Biopsy
SML	Social Media Listening
SMR	Social Media Review
SRM	Standardised Response Mean
SRMR	Standardised Root Mean Square (residual)
SRPB	Spirituality, Religion and Personal Beliefs
TAH	Total Abdominal Hysterectomy
TCIs	Threshold for Clinical Importance
TNF	Tumour Necrosis Factor (receptor)
UK	United Kingdom
US	United States
VBT	Vaginal Brachytherapy
WCSQ	Worthing Chemotherapy Satisfaction Questionnaire
WHO	World Health Organization
WHOQOL	World Health Organization Quality of Life

List of Figures

List of Tables

Part I

Concepts and Definitions

Defining Quality of Life

1

Angelos P. Kassianos and Stephanie Tsounta

Contents

Since the 1940s, the concept of quality of life (QoL) started to encompass both positive and negative aspects of life [1]. Prior to that, we were conceptualizing a healthy person as someone who was not sick. The need to investigate QoL further, stemmed from the realization that in the absence of sickness does not exist healthiness. As a term though, QoL is overly general and encompasses many aspects of a person's life which are beyond their health alone.

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1.1 Defining Quality of Life

Calman [2] refers to QoL as a difficult concept to be defined and measured. QoL tools measure the time-specific difference, or gap, between the expectations and hopes of an individual and the actual present experience. According to this conceptualization, QoL can be precisely described only by the individual and must take into consideration many facets of life, well-being and health. The terminology covers not only the influence of the treatment and its side effects but also the patients' understanding and experience of their own functionality. The definitions of QoL always depend on present lifestyle, previous experiences and hopes for the future, dreams and ambitions, and can only be measured in the individual's terms. In fact, QoL usually changes over time and depends on specific circumstances. "High" or "good" QoL is usually expressed in terms of happiness, contentment, satisfaction, and the capability to cope. Therefore, this early definition by Calman emphasizes the importance of personal development for each individual.

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Another definition of QoL is based on De Haes et al. [3] and can be introduced into debates on how to define QoL. According to De Haes et al., QoL refers to the goals of treatment, and the patients' journey for cure. They also suggest that patient's survival as well as their well-being must be considered in depth during health care. In this context, studying QoL can be meaningful in many ways, such as for understanding how patients react to cancer diagnosis and cancer treatment, the interrelations of different reactions, and the patients' overall QoL. At the same time, QoL data can also contribute to resolutions about the efficiency of the therapy and toward improving supportive care for patients with cancer.

Similarly, Revicki et al. [4] refer to QoL as the subjective experiences, states, and perceptions connecting to one's overall well-being. As a consequence, Crosby et al. [5] introduced the features of the physical, psychological, social, economic, and political environment that patients experience. The introduction of facets of QoL pertain to different aspects of patient characteristics and experiences: (1) the population's aging and the resultant increased prevalence of chronic diseases, (2) the agile role played by patients who receive medical care and their interest in the non-clinical parts of the treatment such as QoL, and (3) the realization that many chronic disease treatments often tend to fail to cure the disease, placing an increasingly significant role of QoL.

1.2 Defining Health-Related Quality of Life

What this handbook emphasizes is health-related quality of life (HRQoL), which is considered an important aspect for patients during their treatment and was introduced in the 1980s as a concept. HRQoL is different than QoL and other concepts such as well-being and is defined by the US Food and Drug Administration as a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life. Moreover, HRQoL differs from QoL because it considers aspects of QoL that affect, either physical or mental health [6–9]. Therefore, HRQoL is usually examined in terms of its facets and symptoms and it is considered to affect patients' overall well-being and survival, whereas QoL has a more generalized meaning [10].

HRQoL is an umbrella definition for a wide range of patient-reported outcomes such as health status or living circumstances. Nevertheless, Ferrans recognized some issues surrounding the HRQoL concept. For example, HRQoL is used to differentiate aspects of life from those that are beyond the realm of health care, such as education or public safety. Similarly, and to differentiate HRQoL from QoL, Spilker and Revicki [11] created a taxonomy for non-HRQoL, composed of four areas: personal-internal, personal-social, external-environment, and external-societal environment. Thus, characteristics of a person's healthy QoL may not contain physical, emotional, or biomedically defined health but rather social relationships or financial success.

Sitlinger and Zafar [12] examined cancer patients' HRQoL in terms of how they experience physical, psychosocial, and financial burdens. They found that physical burden is the first facet that most of the patients will often reference when they discuss their QoL. For example, most of their questions address physical symptoms, such as fatigue and weight loss. In addition, the composite scores of HRQoL and physical symptoms are important towards several patient outcomes including survival. On the other hand, psychosocial burdens can be also devastating and can affect the quality of the patient's life. Finally, the financial toxicity is also considered a key facet of cancer care according to patients. For example, through their treatment, some patients develop financial toxicity, which seems to play a crucial role in their overall life. Furthermore, the World Health Organization (WHO) considers that HRQoL is a primary element of QoL in describing an individual's overall condition [13].

The definition of HRQoL provided by Karimi and Brazier [14] is a concerning cognitive judgment of contentment with one's life and an individual's perception of their perspective in life in the context of the culture and value systems in

which they live and in relation to their purpose, expectations, standards, and worries. More specifically, they identify four definitions for HRQoL. First, HRQoL can be defined as how well a person operates in their life and their perceived well-being in terms of mental, physical, and social domains of health. Operating, means their ability to carry out some predefined activities, while well-being refers only to an individual's personal feelings. Second, as opposed to QoL, which is an all-inclusive idea incorporating all aspects that impact upon a person's life, HRQoL consumes only those factors that are part of an individual's health. For example, economic and political circumstances are not included in this definition of HRQoL. Third, the HRQoL definition is focused on those aspects of QoL that are influenced by health. For example, HRQoL is stated as those aspects of self-perceived well-being that are related to, or affected by, the existence of an illness or therapy. Fourth, HRQoL, focuses on the value of health referring to the values allocated to different health conditions like cancer.

Why is it important to consider HRQoL? By analyzing HRQoL data we can identify those individuals or communities of patients that present with relatively poor perceived health and guide interventions towards improving their lives and preventing more serious consequences for their lives. Moreover, publishing HRQoL data can help shape health policies and legislations, allocate resources, develop strategic plans, and monitor the effectiveness of interventions such as drugs and psychosocial interventions. However, the HRQoL literature also presents some limitations. For example, some HRQoL questionnaires measure self-perceived health status and the use of the QoL terminology usually can be unclear in many scientific publications.

In the following chapters, the concept of HRQoL will be considered together with debates on how it is measured, how it is used in clinical trials, how it can improve health care, or how it can be used to inform health costs, among others.

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The Importance of Quality of Life in Cancer Patients

2

Stephanie Kyriacou

"I never really knew what 'chemotherapy' meant, but it had the words *therapy* in it, so I expected it to be *therapeutic*" was a statement uttered to me by a patient which will always stay with me. "Little did I know my life would feel anything but healed during it," he continued. This 50-year-old stage IV, lung cancer patient, decided to end a rigorous chemotherapy treatment after 6 months under it. Andrew[1] died 2 months after this statement, but in our last meeting while lying in his bed he confirmed to me that he was "comfortable" and that he was able to spend his waking hours with his family, and not attached to tubes in a faraway hospital, or constantly being sick. He had a beautiful relationship with the ocean, so in these last few months his wife had made sure to drive him to the sea as often as possible; something he was able to do once his schedule freed up from appointments. It was clear that Andrew was looking for some quality in his life. There was a possibility that more longevity would be attained had he continued chemotherapy, but Andrew felt that quality of life (QoL) super mounted the extra days, weeks, or maybe months he would gain, if that "gained" time would have been of poorer quality.

Allow me to also introduce you to Ella,[1] a 45-year-old, stage IV pancreatic cancer patient. At every meeting, Ella would ask me, "Do you feel a lot worse before you get better?" or she would exclaim with a strength I have not often encountered in my practice, "I think I'm feeling better today, maybe this is working." Ella was visibly emaciated and while not always admitting it, under a tremendous amount of constant pain. Ella was receiving one form of treatment until her very last week. It seemed that she chose longevity of life (LoL) over QoL, even if that meant she was unable to move for 5 months, or that she lost the ability to feed herself. Ella had two teenage daughters and a doting husband. It is probable that she survived those 2 years, *because* of the treatments she received. Did her gained longevity justify the reduced quality of her life? Only she and her family can answer that question; a question the family often explored with me after her death and through their grief. What makes a patient like Andrew choose QoL over LoL? What made Ella choose the alternative? At what point do patients make this choice?

The factors that affect any patient choosing QoL are multi-faceted and dynamic: meaning it is not usually based on a single factor and similarly, it can change over time. The patient's baseline QoL plays an important role. What did

[1]The names of the patients and the diagnoses have been altered to protect confidentiality.

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Andrew's life look like before the physical exacerbation? Societal and/or cultural relationships to death, suffering, pain, or disease can also genuinely, and sometimes unconsciously, predispose someone to certain choices. Cyprus is a small, relatively homogenous island, where I have seen that values and expectations can be similarly shared by many; and while the choice between QoL and LoL can be somewhat predictable, cultural predisposition cannot singularly account for such choices.

A family structure and the *importance* that family has on the patient plays a highly important role. A patient with little to no family members surrounding them, may be quicker to opt out of LoL, as they may feel like they have "no one to fight for." Conversely, a person with very close ties to their family, may not want them to witness their suffering and therefore reinforce as much quality into their life while trading off duration. Did Ella choose to live longer but poorer, because she wanted more time with her daughters? Very possibly. Would her decision be different if she was 20 years older and therefore by default so were her daughters? Another possibility, which brings me to the next factor. The patient's chronological age can play a huge role in not only the patient's QoL, but also the consultant's suggested course of action. The latter brings me swimmingly into my next factor which greatly affects QoL: the patient's understanding of their cancer, the treatment, and prognosis.

If you recall Andrew's statement above, he states "I never knew what chemotherapy meant…". One can argue that should he had had a better idea about his disease and its progression, he would have made different choices from the start. In my clinical practice, I have often seen a face of surprise (or is it relief?) when reminding the patient that they have a right to choose their treatment (or non-treatment) as well as the right to talk to their consultant about how cancer or its treatment is affecting their QoL. Giving the patient space and allowance to talk to their consultant about their QoL, choices and expectations may help give the patient a sense of agency, and therefore they can make a truly informed decision. In a time when a person loses control of nearly every facet in their life, be that physiological, occupational, or societal, instilling a sense of control and choice in the patient's life can, in and of itself, improve their quality of life, irrespective of their choice.

Clinicians have a large influence over a patient's final decision, so it is therefore of vital importance that the patient has a full understanding of their cancer, its treatment, and the impacts it may have on their life in its totality. Only then can a patient undergo the internal dialogue of what compromises and trade-offs they are willing to make. While clinicians undoubtedly and inherently know that quality of life plays a huge role, it is important to take note of their own and more importantly, the patient's *definition* of QoL. What did QoL mean for *Andrew*? It seemed it was one where he was still able to spend hours at the seaside any day he desired. What did quality of life mean for Ella, for Helen, or for George? This brief dialogue could easily put both parties on a pathway of open and honest communication, one which can lead to a less tumultuous road, with much better views.

How does one address the quality of life needs of a patient? As a psychologist you not only can help identify the needs of the patient, but you can also set the patient up for exploring this question in the first place. It is often the case that patients have not even had this internal dialogue, of what *really* matters to them and how it could possibly materialize. Addressing the QoL needs of a patient could be as simple as a timely referral to better pain management. In another case, it could involve being the bridge between the patient and his family members when their wishes differ on a fundamental level. Similarly, it could mean working on the family's acceptance that their loved one has reached a stage of palliation, the end of their life. Lastly but by no means least, it could involve having a discussion about their values and proposing ways where their actions can somehow be in concordance with these values. Andrew worked on the sea every day. He was a boat technician, a sailor, and as a hobby he was a scuba diver. He may not have been able to scuba dive anymore, but he was at least able to watch the sea, taste the salt, and feel its air. This was

good enough for Andrew in those last few months of his life. Being able to do that with his wife gave him meaning and dignity in the end.

Addressing the QoL of a patient should be done whether they are palliative or not, whether the person is elderly or young, whether they had a "good" life before, or a "bad" one, whether they have five kids, or none. Desiring QoL can seem so obvious or implied, that it can be inadvertently neglected by not allowing the patient to define what it means to *them.* Perhaps a better term instead of the generalized QoL, could be Quality of *Their* Life, where we simply add one word to remind us as their doctors, as their family, as their therapists, that it is *their* life, and the only person that can define it is the person going through it. So, let us start a dialogue, and a frequent one at that: What does quality mean in *your* life?

Part II

Quality of Life Assessment

3 Using the WHOQOL as a Generic Measure to Assess Quality of Life During Cancer

Brenda L. Den Oudsten
and Suzanne M. Skevington

Contents

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3.1 Introduction

Quality of life is generally a major concern for people who are diagnosed with cancer. As cancer now affects one adult in two, living in Britain today [1], designing reliable, valid assessment tools that can sensitively monitor changes in quality of life (QOL) throughout treatment and beyond is essential to being able to deliver the best care to patients. Underpinned by a definition

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of QOL published by the WHOQOL Group collaboration at the World Health Organization (WHO), a suite of WHOQOL instruments were developed so that adults could report their own quality of life (QOL) in a meaningful way. The WHOQOL Group designed a novel cross-cultural methodology to simultaneously create highly equivalent multiple language versions in 15 cultures, applying an internationally agreed protocol [2, 3]. Qualitative input from focus groups in these cultures informed the global concept and the contents and format of two "core" instruments that were later standardized internationally using psychometric methods: the WHOQOL-100, and its short form, the WHOQOL-BREF [4]. These core measures assessed 25 dimensions or facets of QOL. Using cultural adaptation and translation procedures, the WHOQOL-BREF is now known to be applicable and acceptable to people in around 200 cultures worldwide living in very varied situations, and for use by almost all clinical and non-clinical populations that can self-report their own QOL. The EUROHIS QOL 8-item index has also been extracted [5].

Several add-on specific modules were later developed which contained specific facets known to be important to a particular population. They were designed to be bolted onto a core measure, so that they completed the full concept of QOL for that population by including issues that were important to them. These modules included a version for people over 60 years (The WHOQOL-OLD), people with disability (The WHOQOL-DIS), pandemic infections like HIV/AIDS (WHOQOL-HIV), pain (The WHOQOL-Pain), and to expand the Spiritual QOL domain on Spirituality, Religion, and Personal Beliefs (SRPB) (The WHOQOL-SRPB). The new WHOQOL-Combi [6] expands the original multidimensional concept in the WHOQOL core, from 25 to 36 QOL facets, thereby offering a more detailed understanding of that person's QOL.

The core WHOQOL instruments have acceptable good psychometric properties in many culturally appropriate language versions where they have been standardized. A considerable body of research further shows that the core measures provide sound evidence when measuring subjective QOL in many types of cancer, as we shall show. The "subjective" approach in measurement contrasts instruments like the WHOQOL with "objective" aspects of QOL assessed by other tools, such as counting symptom frequency, the consequences of having a disease, and the adverse effects of medical treatment. By co-administering a subjective assessment with an objective measure, a more comprehensive and clinically useful assessment of that patient's QOL is acquired.

This chapter enables readers to learn more about (a) the conceptualization of QOL according to the WHOQOL perspective; (b) the WHOQOL instruments, including their psychometric properties, its use in clinical practice and scientific research, and their pros and cons; (c) the comparison between the WHOQOL approach with the EORTC approach; and (d) different scientific studies using the WHOQOL instruments in the field of cancer.

3.2 Conceptualization of Quality of Life

Patient-reported outcome measures are increasingly important in oncology since they assist us to deliver care for patients so that their outcomes are optimal. Three main types of patient-based outcomes have been identified: quality of life (QOL), health-related quality of life (HRQOL), and perceived health status (HS) (see also Chap. 2, this volume). Most experts now agree that these QOL concepts are not one dimensional, from good to poor, but multidimensional to reflect how people think, and contain important domains like physical, psychological, and possibly social QOL. Operational definitions of related concepts (i.e., HRQOL and HS) are not equivalent to the definition of QOL [7, 8]. In short, HRQOL and HS are bound to health, while QOL is broader than health. Health status refers to physical and mental abilities and social functioning, but without an evaluation of these aspects [9, 10]. HRQOL is QOL, but more narrowly defined as related to health [9, 10]. QOL reflects the affective and cognitive responses to the align-

ment or discrepancy between a person's standards, goals, and values on the one hand, and the actual situation and their accomplishments on the other hand. According to the World Health Organization Quality of Life (WHOQOL) Group, QOL is defined 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 person's physical health, psychological state, personal beliefs, social relationships and their relationship to salient features of their environment"* [11]. In other words, QOL is considered to be "*in the eye of the beholder*" and represents the person's subjective evaluation of one's social and material world. It also reflects the extent to which the individual is satisfied with, or bothered by, problems in a wide range of life domains [12, 13], so the inquiry into QOL includes both a positive approach, as well as negative dimensions [11].

During its debate about the concept, the WHOQOL Group distinguished between different levels of questioning, and sleep provides an example of different ways in which QOL has been assessed. First, electrical brain waves during sleep can be monitored by the electroencephalograph (EEG), and records of this electrical activity represent objective information about QOL. However different types of perceptions also provide insight into QOL. Perceptions of objective features might include inquiries about functioning, like sleep length, (e.g., "How many hours did you sleep last night?"). However interpretation is involved to find out about QOL from the answer to this question [14]. Does 12 h sleep every night indicate good or poor QOL? What about 4 h sleep? British Prime Minister Margaret Thatcher flourished on 4.5 h sleep, but others find this amount distressing. This perceived objective information could lead to inaccurate assumptions about QOL if clinicians omit to also ask patients about how they interpret the number of hours they sleep. Is it bothersome, or not? While information about sleep length, interruptions to sleep, early waking, medication use have considerable value in achieving other clinical goals, this information alone does not provide direct insight into the person's QOL, because it requires interpretation. To obtain an essentially subjective view of a person's QOL, it is necessary to ask a question like "How *refreshing* is your sleep?" Waking refreshed is more important to a person's QOL, irrespective of the number hours they sleep. Yet other styles of subjective questions request highly personalized evaluations of functioning (e.g., How satisfied are you with your sleep?). The WHOQOL group argues that these different types of perceptual information best inform us about QOL [3]. As such, the WHOQOL instruments only cover interpretations of a few symptoms like pain, sleep, negative feelings, and exclude direct measurement of the consequences of disease, and adverse effects of medical treatments [15], but instead, their impact on QOL. Although these aspects can influence patients' lives, the WHOQOL group decided to measure the perceived impact of them, by assessing its influence on each QOL domain and its facets. However, assessing symptoms, disease consequences, and adverse side effects of treatment can be obtained by co-administering another standardized instrument with the WHOQOL. While the WHOQOL Group developers acknowledged that these aspects can and do influence patients' lives, they decided to measure their perceived influence on different domains (and their component facets) of QOL [15].

3.3 Overview of the WHOQOL Suite of Instruments

The WHOQOL core instruments – WHOQOL-100 and WHOQOL-BREF [4, 16] – can assess QOL in a wide variety of situations and population groups. The 100 items of the WHOQOL-100 provide a suitable instrument for the comprehensive assessment of QOL, especially in clinical and other types of research. The 26 items of the WHOQOL-BREF (extracted from the WHOQOL-100) offer a shorter developed measure that is easier to implement in clinical practice and large-scale surveys [15]. One

item is included from each of the 24 facets of QOL contained in both core measures, together with two additional items that combine to assess overall QOL and general health. The multidimensional nature of QOL is reflected in the structure of these instruments. The WHOQOL-BREF facets are organized in four broad QOL domains: physical health, psychological state, social relationships, and environmental QOL. The WHOQOL-100 contained six domains, including a level of Independence domain which was later subsumed under physical health in the WHOQOL-BREF, and a domain on Spiritual QOL, which was integrated into psychological state.

It is not widely appreciated that it is also possible to ask about the importance of each aspect of QOL by administering the WHOQOL Importance scale, which contains items corresponding to every facet. This measure was developed during the WHOQOL-100 project [17]. Importance data from 15 countries informed the selection of the most important QOL facets from a large pool, for testing in the international measure. Several studies have used these evaluations of importance [17–20]. One study focused specifically on community adults dealing with a potential cancer diagnosis [19]. Unlike some measures arising from the economics field, importance data is not used to weight facet and domain scores of the WHOQOL instruments, but it is clinically interesting in its own right. The WHOQOL Group introduced the EUROHIS-QOL 8-item index [5]. Like the WHOQOL-BREF, this scale was derived from multicultural WHOQOL data ($n > 20{,}000$) and contains two items from four domains: physical, psychological, social, and environment [5, 21]. The instrument shows good cross-cultural performance, and satisfactory convergent and discriminant validity [5, 22].

Add-on modules of items were later developed in similar collaborations to permit more comprehensive assessment of QOL for specific populations (e.g., the elderly [23]; persons with disability [24]); infectious diseases, namely, HIV/AIDS [25, 26]; problems of pain and discomfort [27]; and expanding the existing spirituality, religion, and personal beliefs (SRPB) domain [28]. During the 1990s, the WHOQOL group was interested in developing an international cancer-specific module, but this did not progress beyond the preliminary stage [2].

In 2020, Skevington et al. reassessed the suite of WHOQOL measures and modules. They selected one item from facets in the modules and combined them with all WHOQOL-BREF items to form a new generic instrument called the WHOQOL-Combi [6]. In a study of older adults, they showed that the WHOQOL core concept was enhanced by adding these new generic dimensions drawn from other WHOQOL modules. This work has provided a WHOQOL measure of intermediate length, with more elaborate multidimensionality. Module facets like social inclusion (HIV/AIDS module), use of time, and intimacy (WHOQOL-OLD) are potentially relevant to other diseases and conditions, the general population, and younger people. The WHOQOL-Combi contains 38 items; 36 specific items with standard general QOL items on overall QOL and health. By adding these new items, the domains contain more equal numbers of facets (six to eight) than in the WHOQOL-BREF, thereby improving domain equivalence. The preliminary psychometric properties of the WHOQOL-Combi are promising.

3.4 Comparing the WHOQOL Instruments with the EORTC QLQ Measure

The EORTC QOL Group has developed a cancer-specific QOL measure known as the EORTC QLC C30 as their core instrument (see also Chap. 5, this volume). This can be combined with additional cancer-specific modules as needed, such as the EORTC QLQ BR23 for assessing breast cancer. The approaches taken by the WHOQOL and EORTC are similar in certain aspects. In both cases, multiple centers simultaneously participated in establishing new instruments, and stakeholders including patients, provide input about which topics should be assessed. However, there are also differences. The website of the EORTC

QOL group presents several definitions of QOL. It is not clear what definition they own, and which one was used as theoretical guidance to the development of their instruments. The manual points out that patients are asked about their health, and the experiences they had as a result of treatment or disease. If there is already a list of consequences, patients are asked to indicate for each experience, to what extent they experienced it during their illness. Inspecting the items shows the focus is more on the symptoms (e.g., did you have hot flushes?), consequences of cancer, or the adverse effects of treatment (e.g., have you lost any hair?), than perceptions. In the EORTC QLQ C30, there is only one item on how persons would rate their QOL. As such, the EORTC instruments tend to focus more on negative aspects than positive aspects in life, compared to the more positive approach in the WHOQOL instruments. Some items, such as "have you lost any hair?" could be considered as an objective item, since one is able to observe whether someone has lost hair. Moreover, a response on this item, will not inform about the impact of hair loss on that person's life. Compared to the WHOQOL approach, this is different as well. This focus may be explained by the fact that the EORTC instruments are primarily designed for use in clinical trials where there is considerable emphasis on recording the adverse effects of treatment.

3.5 Psychometric Properties of the Core WHOQOL Instruments

When the core WHOQOL instruments were developed, participating centers were asked to deliver a required sample size with sufficient diversity. A sampling quota was specified with regard to age, gender, and health status. Ill people represented the health-care users of their country or region, and reported a wide range of diagnoses of varying disease severity and disability [2, 11]. Consequently, the WHOQOL instruments are assumed to be suitable for different populations (e.g., generic population, elderly, healthy persons), and settings (e.g., rural or industrialized areas). Various researchers have psychometrically tested these instruments in diverse cancer populations (for more information on psychometrics see Chap. 7, this volume). These include breast cancer [29–31], lung cancer [32], sarcoma [33], advanced cancer [34], comparing QOL in different cancers (e.g., liver, lung, colorectal, gynecological, head and neck) [31, 35], and treatments like radiotherapy [36]. Although most research has recruited cancer patients receiving secondary or tertiary care, it is useful in primary care as it was also developed to be used in the "healthy" populations. For instance, it has been used to assess the QoL of those receiving mammography screening (e.g., [37–39]).

With regard to the WHOQOL-100 [29, 31, 33], confirmatory factor analysis showed a good structure with models reflecting six factors that corresponded with the established domains of physical, psychological, independence, social, environment, and spiritual QOL in breast cancer [29]. Furthermore, the alternative four-factor structure (physical, psychological, social, and environmental QOL) was adequate for breast cancer and also for a heterogeneous sample combining head and neck, and breast cancer patients [29, 31]. The WHOQOL-100 correlated highly with related constructs and low with unrelated constructs [29] in two similar questionnaires: the EORTC QLQ B23 [29] and General Quality of Life Questionnaire [31]. For instance, relevant to breast cancer, the body image subscale of the EORTC QLC BR23 correlated highly with the body image and appearance facet in the WHOQOL [29]. The internal consistency of facet and domain scores was adequate as shown by Cronbach's alpha coefficients that exceeded the acceptance criterion of .70 [29, 31]. Test-retest correlations were high in both breast cancer and sarcoma [29, 33]. Based on the WHOQOL-100 scores, it was possible to discriminate between healthy people and persons with sarcoma [33], and in other groupings with various diseases including cancer. The reliability and validity of the WHOQOL-BREF was also adequate, although the internal consistency (Cronbach's alpha) of the social relationships domain tends to be just below .70 in some studies (e.g., [30]).

Where patients were treated with radiotherapy, the researchers noted that not every cancer patient was able to complete the WHOQOL-BREF THAI on their own [36]. Common reasons for this occurrence are physical disability in the hands, and limited literacy which restricts independent self-reporting. The measure can be interviewer administered, if available.

3.6 Using the WHOQOL Instruments in Research and Clinical Practice

During the development phase of the WHOQOL core, potential uses of these instruments were discussed and described. These included medical practice, research such as clinical trials or epidemiological studies, audit [40], policymaking, and assessing the effectiveness of an intervention or treatment, or the relative merits of several treatments [41]. In medical practice, the WHOQOL instruments provide valuable information on those life domains which are most affected. Instruments can determine a baseline score at the time that a treatment [42], a trial (e.g., [43]), or a longitudinal study begins [44]. Scores can also show how QOL develops during the course of treatment or an intervention, but they can also assess late problems [45].

By increasing understandings of how the disease affects a patient's QOL, this information has been used to improve the interaction between the patient and their health-care professionals [20, 46], and may even improve their relationship. In addition, it helps health professional and patient make optimal choices about patient care [47]. Moreover, it can assess any changes and provide insights in how different QOL domains are affected over the course of treatment [47], even if computerized assessment is used [48]. In primary care, discussing QOL results and the importance of different dimensions of QOL has shown that 65% report changes in their thoughts and perceptions. Half the participants in this study evaluated this QOL feedback as helpful [20].

Recently, Greenhalgh et al. conducted a "realist synthesis" aimed at understanding how, and in what circumstances, patient-reported outcome measures (PROMs) like QOL assessment, support patient-clinician communication, subsequent care processes, and outcomes of clinical care [49]. Two theoretical ideas about how this process works was tested. First, the completion of PROMs prompts a process of self-reflection and supports patients to raise issues with health professionals. Second, empirical data from PROMs scores raise health professionals' awareness of patients' problems, thereby prompting discussion and action. The results showed that using PROMs does prompt patients to reflect on their health and gives them permission to raise issues with their clinicians. However, health-care professionals (HCPs) sometimes found that administering standardized PROMs for completion during patient assessments did not support communication. Where this occurred, HCPs changed how they used PROMs to render them compatible with the ongoing management of patient relationships. Using PROMs supported dialogue, by enabling patients to tell HPCs what is on their mind. In oncology, PROMs completion outside the consultation enabled HCPs to identify symptoms when the PROM acted as a substitute, rather than addition to the clinical encounter. They also found it helpful when the PROM focused on symptoms and side effects. However, patients did not always feel it was appropriate to discuss some QOL aspects with their HCP, and some HCPs did not perceive that this was within their remit [49]. In another study by King et al., a systematic review and interviews focusing on brain cancer were conducted [46]. They concluded that the evidence on the effectiveness of using QoL tools was inconsistent for patient management, but it was somewhat more consistently in favor of improving patient-physician communications. However, these tools were not currently widely used in clinical practice in brain cancer, nor some other cancer contexts. More implementation studies are needed.

Cancer treatment, like chemotherapy, may prolong the patient's life. However, it may also negatively affect that person's QOL. A recent community study [19] investigated whether feeding-back personal QOL information could

change QOL when a potential cancer symptom is present. The researchers also examined whether poor QOL at the time of increasing cancer awareness promoted attendance in primary care. Patients were randomized into an intervention group, who received feedback about their QOL, or a control lifestyle group, who just completed QOL measurements but did not receive feedback. This study found that persons who received feedback reported improvements to their psychological QOL, reflecting better mental health. However, the number of visits to a general practitioner was unaffected. Nevertheless, feedback did increase help-seeking from their informal social contacts. The authors concluded that their study offers new evidence that at the earliest, pre-diagnostic stage of cancer and QOL feedback may stem QOL deterioration in those with potential cancer symptoms during the period before they consult in primary care.

In research, the nature of a disease can be determined by assessing how a disease like cancer impairs or affects the subjective well-being of patients across important life domains. In this case, QOL can be used as a secondary endpoint in clinical trials [42]. Another option is to use QOL instruments as a prognostic tool to determine the overall response of the patient to treatment [50], overall survival [42], or to predict mortality [45]. For instance, Schwartz and Sprangers suggested that a QOL assessment could be included when it is expected that survival will be gained at the expense of QOL [45]. Interesting as well is to monitor how QOL evolves across time, also, in cases where disease prognosis involves remission, or when treatment becomes more palliative than curative. The cross-cultural WHOQOL measures also have considerable value where it is necessary to accumulate cases, as for example, when studying rare types of cancer. In this case, gathering data from several institutions across the world enables statistical tests to be performed reliably on pooled data, in ways that would not be feasible on one very small sample from a single nation. Multicenter studies can provide parallel replications simultaneously, thereby accelerating scientific progress and implementation by adding confidence to the conclusions [41]. Another application is to measure QOL variation across different cultures and examine similarities. Where there are multiple language versions of the same measure, like the WHOQOL-BREF, this facilitates comparisons between cultures. This information could assist policymaking and underpin service delivery. As the profile of domain scores generated by WHOQOL core measures is sensitive to changes in clinical conditions across time, so is responding to changes in health [51].

When health-care services need evaluation, QOL assessments can be used to measure the relationship between health-care service delivery and the QOL of patients who receive it. Furthermore, these data can be used to study the effect of implementing new policies and making changes to existing policies on QOL. Using the WHOQOL allows monitoring changes in QOL for every domain in the profile. This information has been used to review the quality of medical services [41] and could be readily applied to physiotherapy, social, psychological, and most other services. From 2011, the WHOQOL-BREF was administered annually to those receiving mental health-care services delivered by the entire State of Connecticut in the USA (DMHAS) [52]. Through disaggregating population subgroups using survey results on demographic characteristics, treatments, sites, and other features, they can identify and pinpoint which ones are being disadvantaged by existing services provision. Annual administration of the WHOQOL-BREF has enabled them to monitor whether the QOL of clients in these disadvantaged groups has subsequently improved. Moreover, DMHAS utilizes this internal empirical information to reallocate and redirect the budget, in order to remedy these evident shortcomings. These reports and subsequent actions become public information [52]. However, it remains unclear to what extent the WHOQOL instruments are actually used in this way, as this kind of information is not published in searchable databases.

3.7 Quality of Life Assessment Within the Field of Oncology

To the best of our knowledge, Tazaki et al. were the first to use the WHOQOL perspective to assess cancer patients [53]. They evaluated eight groups of cancer patients, classified in terms of cancer stage (early vs. advanced), current treatment (ongoing vs. none), and prognosis (good vs, bad), and studied differences in site, treatment, and gender role [2]. This study showed that patients with bone and cartilage cancers reported significantly lower independence QOL, than those with female genital organ cancers. Lymphoid, hematopoietic, and related tissue cancer patients had lower psychological QOL than digestive system cancers. Patients receiving chemotherapy had significantly lower psychological QOL than those without. Women reported lower psychological QoL than men.

Tables 3.1 and 3.2 provide an overview of studies and their main findings in which WHOQOL instruments were used within the field of oncology. Given the number of studies and space limits for this chapter, only studies with multiple assessments across time (Table 3.1) and intervention studies (Table 3.2) are reviewed. The studies can be divided into comparisons between (i) different diseases [e.g., 55] including cancer, (ii) different medical treatment options [e.g., 54], (iii) different instruments, (iv) cancer patients with a norm population [60]. We also consider (v) sociodemographic and clinical factors predicting QOL [e.g., 47], (vi) development of QOL across time [e.g., 54], (vii) assessing the consequences of medical treatment [e.g., 59], or (viii) the effectiveness of, for instance, counselling [e.g., 43], exercise [e.g., 95], or a lifestyle program [e.g., 76].

The published literature in Tables 3.1 and 3.2 (extracted from PUBMED) shows that more than 392,000 people with cancer have completed a WHOQOL core measure. The total recruited is testament to the acceptability of these measures; indeed, and one study of breast and prostate cancers [74] explicitly tested and affirmed this feature. Diagnostic groups investigated include breast cancer (16 studies), also cancers of the head, neck and mouth, lung, colorectal, prostate and bladder, thyroid, liver and kidney, and gynecological sites. These studies were conducted in some very different cultures worldwide. Culturally adapted translations of WHOQOL instruments administered to cancer patients include Dutch, Chinese (also culturally adapted for Hong Kong and Taiwan), Hindi (India), Farsi (Iran), Spanish (Colombia), Swedish, Portuguese (adapted in Brazil), Japanese, Thai, Vietnamese, Korean, Indonesian, Malaysian, Polish, Italian, Croatian, Greek, Czech, Turkish, and English (UK and US) language versions.

Most studies showed that QOL was barely okay, and often poor in people with cancer at the time of recruitment, irrespective of whether this time was a baseline before treatment (e.g., chemotherapy, surgery), an intervention (e.g., exercise), monitoring a stage of cancer, or just time. This conclusion is also supported when these values are compared with adjusted means gathered from healthy, and sick groups including cancer, that contributed to heterogeneous international [5, 12] and national data (e.g., [36]), for the purposes of standardization. Where domains show significant changes over time, not only do the physical and psychological QOL domains reflect improvement, as expected, and similar to other measures, but significant changes in environmental and social QOL are visible too. In a large study ($n = 2120$) where a mixed groups of cancer patients received a cancer management intervention, all four domains and overall QOL and health, significantly improved [79]. These results illustrate the value that the WHOQOLs breadth of concept provides. These collected results also offer evidence that the domain scores change sensitively in response to changing health, thereby demonstrating an important measurement property that is valuable clinically. The size and type of sample, study context, and the nature of an intervention will potentially affect which domain scores will show significant change.

Fewer tabulated studies reported significant results for the social domain, which may be the weaker WHOQOL-BREF domain, containing only three items. The new WHOQOL-Combi includes six social items, which has improved the

Table 3.1 Overview of observational studies using the WHOQOL-100, WHOQOL-BREF, or EUROHIS 8-item

Author (Year of publication)	Type of cancer Sample size (*n*) Country in which the study is performed	Instrument	Aim	Findings
Kao et al. 2021 [54]	Localized prostate cancer (PC) (*n* = 196) Taiwan	WHOQOL-BREF and eight WHOQOL facets: pain, mobility, work capacity, negative feelings, respect, daily information, transport, general QOL, health satisfaction	To assess the dynamic changes of QOL in patients with localized PC under different treatment modalities: active surveillance (AS), radical prostatectomy (RP), or radiotherapy (RT)	Patients with lower household incomes showed statistically significant lower scores on all WHOQOL domains and facets. PC survivors with anxiety and/or diabetes appeared to be poor on the physical domain and related facets. After controlling for these variables, patients under active surveillance (AS) showed better physical health and social relationships, as well as several facets belonging to these domains, compared with patients undergoing RP or RT, within the first year. The general QOL scores were higher within the first year in patients receiving AS, after controlling other significant factors. The difference diminished after 1 year of post management
Goossens-Laan et al. 2013 [55]	Bladder cancer (*n* = 102) and other types of cancer (*n* = 29) out of 598 patients with primary hematuria The Netherlands	WHOQOL-BREF	To examine QOL in patients with primary hematuria who later appear to have bladder cancer, and patients with other cancer diagnoses	Patients with bladder cancer have comparable QOL to patients with other diagnoses
Van Montfort et al. 2020 [56]	Lung cancer (*n* = 130) The Netherlands	WHOQOL-BREF	To identify psychological profiles covering multiple psychological factors The association between these profiles with QOL and with sociodemographic and medical characteristics, was explored	Four psychological profiles were identified: (1) anxious, extensive coping repertoire (33%); (2) depressive, avoidant coping (23%); (3) low emotional symptoms, active/social coping (16%); and (4) low emotional symptoms, limited coping repertoire (29%). QOL in profile 1 was significantly different from QOL in profile 3 and profile 4. QOL in profile 2 was significantly different from QOL in profile 3 and profile 4. Sociodemographic and medical characteristics (i.e., tumor grade, clinical stage, and treatment) were not distinctive for the profiles

(continued)

Table 3.1 (continued)

Author (Year of publication)	Type of cancer Sample size (*n*) Country in which the study is performed	Instrument	Aim	Findings
Tang et al. 2012 [57]	Nasopharyngeal cancer (*n* = 46)	WHOQOL-BREF	To evaluate factors affecting QOL of nasopharyngeal carcinoma (NPC) patients with radiation-induced brain injury (RI)	Patients with RI had significantly lower QOL scores in physical health, psychological state, and social relationships compared with those in patients without RI. Anxiety and cognitive impairment were significant predictors of the facet overall QOL and general health
	China		To compare QOL of NPC patients with RI with a group of matching post-radiotherapy NPC patients without RI	
De Mol et al. 2020 [58]	Lung cancer (*n* = 151) The Netherlands	WHOQOL-BREF	To examine the association between sociodemographic factors, personality traits, and depressive symptoms, at the start of chemotherapy	In the multiple regression analyses, depressive symptoms were most often associated with the WHOQOL-BREF domains and general facet, whereas depressive symptoms and performance status were most often associated with the EORTC QLQ-C30 scales. Except for trait anxiety, personality traits were unrelated to these outcomes
Van der Steeg et al. 2010 [47]	Women with breast cancer (*n* = 222), of which 105 were treated with breast conserving therapy and (BCT) and 117 with mastectomy (MTC)	WHOQOL-100	To assess the influence of surgical treatment and personality on QOL in women with breast cancer	Patients treated with BCT or MTC did not differ on overall QoL. At all time points (1, 3, 6, and 12 months after diagnosis), the influence of trait anxiety on overall QoL was substantial in the BCT group. Women who scored high on trait anxiety were 7 times more likely to have a low overall QoL 1 year after BCT. In the MTC group, overall QoL was influenced mainly by neuroticism
	The Netherlands			
Schiavolin et al. 2018 [59]	Neuro-oncology patients undergoing surgical removal of the lesion (*n* = 101)	EUROHIS-QOL-8	To assess surgical outcomes in brain tumor surgery, using patient-reported outcome measures (EUROHIS-QoL, PGWB-S, WHODAS-12) before, and 3 months after surgery	Psychological well-being improved at follow-up. 95 patients (94.1%) were improved/unchanged and 6 (5.9%) were worsened according to PROMs; functional status measured with Karnofsky Performance Score (KPS) had a slight agreement with QOL and disability and no agreement with psychological well-being questionnaires. Patients with complications had a greater worsening in KPS
	Italy		To compare the results with traditional clinical outcome measurements	

Lee et al. 2007 [60]	Hepatocellular carcinoma (HCC; $n = 161$) Taiwan	WHOQOL-BREF EORTC QLQ-C30 Utility measures	To examine QOL in cancer patients	Compared with healthy people, HCC patients had reduced QOL in the physical domains and better environmental QOL. After controlling gender, age, education, and employment, duration of HCC exceeding 1 year was associated with better QOL. Survival over 1 year was associated with better QOL in HCC patients
Vaz et al. 2008 [61]	Gynecological cancer ($n = 95$) Brazil	WHOQOL-BREF	To investigate the incidence of acute toxicity from radiotherapy, evaluate QOL, and identify its predictors	A significant increase in QOL scores was observed in the physical and psychological domains, and also general health and overall QOL. Upper gastrointestinal toxicity and surgery negatively affected general health. Improvement in vaginal bleeding positively influenced general health
Valenti et al. 2008 [62]	Breast cancer ($n = 212$) Italy	WHOQOL-BREF	To assess the association between physical exercise and QOL	QOL strongly decreased during active treatment. Significant correlations were found between total exercise on- and off-treatment, and all QOL indicators. Strenuous exercise was strongly related to QOL. Absent/mild exercise was inversely correlated with a positive perception of disease severity, and with QOL
Den Oudsten et al. 2010 [63]	Breast cancer ($n = 217$), of which 78 needed additional surgical treatment The Netherlands	WHOQOL-100	To examine the effect of multiple surgical treatments on psychological outcomes	Psychological outcomes did not significantly change over time, except for anxiety. On average, women with 1 or 2 surgical treatment(s) did not differ on any outcome measure. None of the interaction effects indicate that changes in outcomes over time were the same for both groups
Den Oudsten et al. 2009 [39]	Breast cancer ($n = 255$) The Netherlands	WHOQOL-100	To examine the relationships of QOL domains to the overall facet across time	Psychological state and social relationships contributed to overall QOL most consistently at the various time points. Physical health was a contributor at all time points, except 1 month after surgery. Environmental QOL contributed less to overall QOL, compared to the other domains. Different facets contribute to overall QOL dependent of particular measurement points. However, the facets positive feelings and personal relationships were important at almost all time points for maintaining a good overall QOL

(continued)

Table 3.1 (continued)

Author (Year of publication)	Type of cancer Sample size (*n*) Country in which the study is performed	Instrument	Aim	Findings
Anton et al. 2008 [64]	Breast cancer (*n* = 120) Croatia	WHOQOL-BREF	To examine the influence of a liaison psychiatric approach on QOL	Liaison psychiatric approach improved QOL in patients with newly diagnosed breast cancer
Mohan et al. 2008 [65]	Non-small cell lung cancer (*n* = 44) India	WHOQOL-BREF	To examine the effect of chemotherapy on pulmonary, nutritional, and QOL	The mean (SD) QOL scores for the physical, psychological, social, and environmental domains were 52.9 (20.5), 56.1 (17.9), 64.5 (21.8), 57.1 (16.6), respectively. There was no significant improvement in pulmonary functions, nutritional status, or QOL scores after treatment
Traa et al. 2015 [66]	Colorectal cancer (*n* = 205) The Netherlands	WHOQOL-BREF	To examine (1) measurement invariance of QOL domains over time for colorectal cancer patients and partners, to investigate, response shift, recalibration, reprioritization, and reconceptualization; (2) between dyad-member measurement invariance; and (3) QOL trajectories Participants completed the WHOQOL-BREF preoperative (Time-0) and 3 (Time-1) and 6 months (Time-2) postoperative	No reconceptualization and reprioritization were detected, but indications for recalibration were present; hence, comparisons were restricted to group-level statistics at factor level. Patients showed a decrease in the physical health domain at Time-1, with partial recovery to baseline at Time-2. For partners, factor means in physical health remained constant, and were at each time point, higher than patients' factor means. Patients' and partners' psychological state decreased at Time-1, but stabilized at Time-2; their factor means were comparable. Patients and partners' social relationship factor means decreased at Time-1, and decreased further for patients, but stabilized for partners. Partners' factor means were only lower than patients at Time-1. Similar decreases in the environmental domain factor means occurred for both patients and partners at Time-1, with stabilization at Time-2
Hyphantis et al. 2011 [67]	Colorectal cancer (*n* = 144) Greece	WHOQOL-BREF	To assess the course of early non-metastatic colorectal cancer patients' QOL. To identify relevant clinical and psychological predictors during 1 year	Paranoid ideation, psychoticism, interpersonal sensitivity, anxiety, and depressive symptoms increased significantly over 1 year. Most QOL domains significantly decreased over the year. General psychological distress and low sense of coherence were independent predictors of QOL. Repression was an independent predictor of physical health

Hyphantis et al. 2013 [68]	Breast cancer (n = 124) Greece	WHOQOL-BREF	To assess psychological correlates of treatment decision preferences and predictors of QOL	Physical health improved significantly and psychological state and environmental QOL remained stable over 1 year. Social relationships deteriorated over the same period. Earlier cancer stage, lower state anxiety, lower repression scores, and improved depressive symptoms predicted improved physical health. Moderation analysis showed that active decisional preferences predicted physical health improvement, but only in women with lower repression levels
Pinell-White et al. 2015 [69]	Breast cancer (n = 129), of which 60 patients completed the follow-up questionnaire at 1 year The United States	WHOQOL-BREF	To describe psychosocial outcomes after breast construction and identify factors that influence them	Compared to the preoperative baseline, overall QOL was unchanged, general satisfaction with health improved significantly, and QOL in physical, psychological, social, and environment domains decreased. Being in a relationship at the time of reconstruction was associated with a decline in overall QOL, as well as social relationships and environmental QOL. Educational level impacted physical and psychological health after surgery. Patients with a higher cancer stage reported decreased satisfaction with health at 1 year. Type of reconstruction, development of a complication, and need for additional surgery did not influence any of these outcomes
Yang et al. 2016 [70]	Non-small lung cancer (n = 336) and healthy referents matched on age and sex Taiwan	WHOQOL-BREF	To compare changes in QOL after three different first-line anti-cancer treatments for advanced non-small cell lung cancer	Performance status was the most important predictor of QOL in all domains, after controlling for potential confounders. Compared with age and sex-matched healthy subjects, patients treated with gemcitabine + platinum showed significantly lower physical and psychological QOL. However, pemetrexed + platinum and gefitinib/erlotinib affected patients' QOL scores in "energy/fatigue" and "daily activities" facets with smaller magnitudes, and scores appeared to improve after 3–4 months of treatment
Badihian et al. [71]	Thyroid cancer (n = 29) Iran	WHOQOL-BREF	To examine QOL in patients with differentiated thyroid cancer either during treatment with levothyroxine or during withdrawal from levothyroxine when whole-body scanning	QOL scores decreased in all four domains physical health: 67.8 to 25.7; psychological: 58.9 to 38.9; social relationships: 67.5 to 56; and environment: 57.2 to 48.8

(continued)

Table 3.1 (continued)

Author (Year of publication)	Type of cancer Sample size (*n*) Country in which the study is performed	Instrument	Aim	Findings
Rzepakowska et al. 2019 [72]	Laryngeal neoplasms (*n* = 137) Poland	WHOQOL-BREF	To compare voice and QOL after microdirect laryngoscopy in benign precancerous and malignant glottis lesions	Only in patients with benign lesions was there a significant improvement in QOL, 3, 6, and 12 months after treatment, in overall assessment of their QOL and general health
De Mol et al. 2020 [73]	Lung cancer (*n* = 69) The Netherlands	WHOQOL-BREF EORTC QLQ C30	To examine the relationship between expectations, feelings about side effects, and satisfaction with therapy and (HR)QoL	Feelings about side effects were associated with social relationships of the WHOQOL-BREF and (HR)QoL in the EORTC
Macruz et al. 2020 [74]	Breast cancer (*n* = 57) Brazil	WHOQOL-BREF	To assess QOL and climacteric symptoms for post-menopausal women receiving hormone therapy	WHOQOL-BREF scores improved by the 6-month follow-up. Correlation of the Kupperman Menopausal Index and WHOQOL-BREF domains showed that less intense climacteric symptoms were significantly associated with higher scores on QOL domains

Abbreviations: *QOL* quality of life, *WHOQOL-BREF* World Health Organization Quality of Life instrument-BREF, *PROMs* patient-reported outcome measures
Note: Studies may have a broader aim than QOL; however, only aims and findings related to QOL are presented

Table 3.2 Intervention studies using the WHOQOL instruments in cancer patients

Author	Type of cancer Sample size (*n*)	Instrument	Aim	Findings
Setyowibowo et al. 2020 [75]	Breast cancer (BC, *n* = 132) Indonesia	WHOQOL-BREF	To examine the effectiveness of a self-help intervention, which aims to improve adherence to diagnostic procedures to reduce the time to a definitive diagnosis	The intervention reduced the time to definitive diagnosis by 13.3 days in the intervention group. No significant differences were found between the groups (self-help intervention vs. usual care) in cancer knowledge, symptoms of anxiety, depression, QOL, or health status
Yang et al. 2020 [76]	Colorectal cancer (CRC; *n* = 68) Taiwan	WHOQOL-BREF	To examine the effect of a healthy lifestyle education program on QOL, ADL, and healthy lifestyle behavior	After controlling for demographic and income variables, significant improvement was found on the facets "overall QOL" and "negative feelings" in the healthy lifestyle education program
Walshe et al. 2018 [77]	Cancer patients (*n* = 85) and persons without cancer (*n* = 72) The United Kingdom	WHOQOL-BREF	To compare QOL trajectories of persons with, and without cancer, referred to volunteer-provided palliative care services	Persons with cancer had a significantly better QOL at referral to the volunteer-provided palliative care services than those with nonmalignant disease, despite similar demographic characteristics. Significant differences in the physical and environmental QOL trajectories between groups were found. Persons with cancer experienced a greater decline in QOL than those without cancer
Elias et al. 2015 [78]	Breast cancer (*n* = 28) Brazil	WHOQOL-BREF	To compare brief psychotherapy (BP), the RIME (Relaxation, Mental Images, and Spirituality) intervention, and control group (CG)	There was a significant improvement (38.3%) after RIME in the WHOQOL, compared with the BP of the CG (12.5%), and the BP of the RIME Group (16.2%)
Funk et al. 2014 [79]	Head and neck cancer (*n* = 46) Brazil	WHOQOL-BREF EORTC-QLC H&N	To evaluate the impact of a dental care program on QOL	Both the test group and controls received basic dental care, but the test group received complimentary care before and during oncological therapy. Dental care was able to reduce damage from the oncological therapy, especially related to mucositis and candidiasis. The test group showed an improvement on the WHOQOL-BREF and EORTC QLQ H&N, while the controls did not change

(continued)

Table 3.2 (continued)

Author	Type of cancer Sample size (*n*)	Instrument	Aim	Findings
Svensk et al. 2009 [80]	Breast cancer (*n* = 41) Sweden	WHOQOL-BREF EORTC QLQ-BR-23	To compare individual art therapy sessions with a control group	Six months after the start of radiotherapy treatment, women who participated in the individual art therapy sessions improved their overall QOL and general health, and environmental QOL compared with the control group. A significant improvement across time was found in all domains, and in overall QOL, general health, physical health, and psychological state in the individual art therapy group. Within the control group, and after adjusting for differences in hormone therapy, a positive difference was found over time in psychological state. Within the individual art therapy group, a significant positive difference in the EORTC QLQ-BR23 domains body image, future perspectives, and systematic therapy side effects occurred over time were found
Ramachandra et al. 2009 [81]	Breast cancer (*n* = 22) and prostate cancer (*n* = 24) The United Kingdom	WHOQOL-BREF	To develop and test a brief, easy-to-use intervention that included the use of a diary, using a mindfulness CD and the planning of a pleasurable activity that could improve well-being and QOL in cancer patients	The intervention was acceptable to users. There was significant QOL improvement post-intervention
Hwang et al. 2008 [82]	Breast cancer (*n* = 40) Korea	WHOQOL-BREF	To examine whether supervised moderate-intensity exercise could mitigate complications that occur during radiotherapy	There were no differences noted at baseline between the intervention and control group. In the exercise group, there was an increase in three domains of the WHOQOL-BREF, not environment. Control group patients showed a decrease in WHOQOL-BREF scores after radiotherapy
Kim et al. 2006 [83]	Gynecological cancer (*n* = 28), Hepatobiliary cancer (*n* = 13) Other cancers (*n* = 12) South Korea	WHOQOL-BREF GHQ-12	To examine the effects of sun ginseng (SG) on QOL	After 12 weeks therapy, psychological state was significantly improved in patients randomized to sun ginseng, compared with placebo. The GHQ-12 total score significantly improved in patients treated with SG than placebo
Lima et al. 2020 [84]	Breast cancer (*n* = 33) Brazil	WHOQOL-BREF	To assess the effect of music interventions on symptoms, adverse events, and QOL	Women undergoing adjuvant CT were randomized into the Music group (GM) or Controls (GC) and followed during the first 3 cycles of treatment. Higher QOL on functional scales were observed for GM compared to GC, after the first and third sessions of CT

Author	Type of cancer Sample size (*n*)	Instrument	Aim	Findings
Periasamy et al. 2020 [85]	Cancer (*n* = 2120) Malaysia	WHOQOL-BREF	To assess the effectiveness of a "Managing Patients on Chemotherapy" book	In this RCT with baseline and 3 follow-up measurements after counseling, the treatment group received counselling regarding chemotherapy by using a developed module. The treatment group improved compared to controls in physical health, psychological state, social relationships, environmental QOL, and overall QOL
Farhadi et al. 2014 [86]	Cancer (*n* = 42) Iran	WHOQOL-BREF	To compare the efficacy of group meaning centered hope therapy of cancer patients and their families on patients' QOL	Group meaning centered hope therapy of cancer patients and their families had a positive effect on patients' QOL compared to the control group. The notable finding was that holding group sessions either for the patients or for their families equally improved patients' QOL
Brozetti et al. 2020 [87]	Renal cell carcinoma (*n* = 26) Italy	WHOQOL-BREF	To examine QOL	QOL analysis, through WHOQOL-BREF questionnaire, assessed at last available follow-up (10 years after surgery) revealed a mean score of 75.9 ± 11.6 on 100 points
Maher et al. 2018 [88]	Cancer (*n* = unknown) The United States	WHOQOL-BREF SF-36	To examine the impact of a 1-week activity-based program on QOL	After 6 weeks, significant changes were found for the WHOQOL-BREF's social relationships subscale. No changes were found for the SF-36 scales
Visser et al. 2018 [89]	Non-small cell lung cancer (*n* = 89) The Netherlands	WHOQOL-BREF EORTC QLQ C30	To explore patient-reported satisfaction with therapy (SWT) and assess its value in addition to QOL and adverse events (AEs)	56 patients (86.2%) would probably or definitely decide to undergo the same treatment again, regardless of deterioration or improvement in QOL, or a high or low frequency of AEs during chemotherapy. The explained variance of QoL by SWT was greatest for the EORTC QLQ C-30 global health status/QoL scale
Pouy et al. 2018 [90]	Breast cancer (*n* = 66) Iran	WHOQOL-BREF	To examine the effect of mindfulness-based group training on QOL	The mindfulness-based group and control group (i.e., received usual care only) did not differ on baseline. However, 2 months after the intervention, the patients in the experimental group reported higher QOL
Longobardi et al. 2019 [43]	Laryngeal neoplasm (*n* = 32) Italy	WHOQOL-BREF	To examine the effect of an intervention that consisted of treatment by a psychologist and speech therapist (experimental group), or treatment with only a speech therapist (control group)	The experimental group showed a significant improvement in WHOQOL-BREF domains on social relationships and environmental QOL

(continued)

Table 3.2 (continued)

Author	Type of cancer Sample size (*n*)	Instrument	Aim	Findings
Li et al. 2019 [91]	Nasopharyngeal carcinoma (*n* = 58) China	WHOQOL-BREF	To evaluate the effect of pregabalin on radiotherapy-induced trismus on QOL	In the treatment group (pregabalin), at week 8, the physical health and the overall QOL life scores of the WHOQOL-BREF significantly increased
Cebicci et al. 2016 [92]	Breast cancer (*n* = 11) Turkey	WHOQOL-BREF	To investigate the clinical effect of extracorporeal shock wave therapy (ESWT) in patients with secondary lymphedema	After ESWT, improvements were observed in the physical health domain of the WHOQOL-BREF.
Bryl et al. 2020 [93]	Pituitary adenoma (*n* = 32) Poland	WHOQOL-BREF	To compare QOL between patients who had undergone either transsphenoidal microscopic (MTS) or endoscopic (ETS) non-functioning pituitary adenoma resection	Treatment groups did not differ significantly in terms of age, sex, tumor size, length of hospital stay, or QOL before the surgery. There were no significant differences in QOL between groups at any stage of the trial. Significantly more patients had improved QOL on the WHOQOL-BREF 3 months after endoscopic surgery
Chang et al. 2018 [94]	Various cancer diagnosis (*n* = 35) Taiwan	WHOQOL-BREF	To compare mindfulness meditation (MM) versus usual care (US) with regard to QOL	The results showed persons in the MM group significantly improved, while there was no improvement in the US group who showed less environmental QOL. There was no significant difference between the follow-up and post-intervention scores in the MM group, indicating that improvement can be maintained for 3 months after completing the MM course

Abbreviations: *GHQ-12* General Health Questionnaire, *ADL* activities of daily life, *EORTC-QLC H&N* EORTC QLQ Head and Neck module, *EORTC-QLC BR23* EORTC QLQ Breast Cancer module

measurement properties of the social domain [6]. The WHOQOL-Combi also offers a distinctive spirituality domain, expanded to six items from one, which increases its relevance to those confronting their mortality, and to the palliative care service in particular. Longitudinal research will be necessary to confirm whether the WHOQOL-Combi is a good tool for monitoring QOL during delivery of the oncology services and across the remaining lifetime.

3.8 Strengths and Limitations of Using the WHOQOL Instruments

The WHOQOL instruments have several strengths, additional to those flagged up elsewhere in this chapter. They place importance on the subjective perceptions of an individual (e.g., satisfaction with their own functioning). Researchers and clinicians who need to know about the patient's view now have a generic tool that we have shown is widely used in the field. While the 100 items of the WHOQOL-100 allow for a very detailed assessment of individual facets of QOL, both core instruments (WHOQOL-BREF and WHOQOL-100) assess QOL with a profile of useful domains that enables users to pinpoint where QOL is poor and good within the physical, psychological, social, and environment domains, by inspecting its component facets. Overall QOL and health is also assessed to provide a global overview. Moreover, as the WHOQOL-BREF contains a compatible subset of items extracted from the WHOQOL-100; this allows for direct comparisons between results collected from either assessment [4]. In some longitudinal studies, the WHOQOL-100 was administered at baseline, then the WHOQOL-BREF used to obtain repeated measures on subsequent follow-up occasions.

The WHOQOL instrument language versions were simultaneously and cross-culturally developed and psychometrically tested from a commonly agreed international protocol. The advantage of such simultaneous development is that the QOL dimensions subsequently included were internationally defined, and thus present in, and relevant to, many very different cultures. Consequently, the facets and domains are known to represent genuinely international concepts of important and recognized QOL dimensions. The danger with just translating an existing measuring is that distorted results may arise from using inappropriate QOL constructs, which are found to be valid and relevant in the source or original, language setting, but not in the target group (or other) language settings. Equally important, there may be QOL aspects that are important to the target culture, but these are not covered in the source instrument [4]. Related to this simultaneous, cross-cultural development is the benefit that the instruments are available in many diverse languages worldwide. As these are psychometrically tested, this feature also makes it possible to compare QOL in countries which have very different health-care systems. The items were drafted based on statements by patients with a range of diseases, by healthy persons, and by health professionals.

In oncology, an advantage of using the WHOQOL tools is its breadth of coverage across the many life qualities of patients and their families. The QOL of family members and other supporters can be seriously affected during the period surrounding the diagnosis and treatment of cancer, as well as during palliative care, and grieving [96]. As the WHOQOL tools have been standardized for use in populations that include "healthy" people, it is useful to administer the same tool to both patient and their family members, so as to understand divergent views, and address distressing misunderstandings. Another advantage is that the WHOQOL assesses QOL over the "*past two weeks*," not "*today*," like some other measures. Given the serious impact of an aggressive treatment on the mood of the day, an assessment covering 2 weeks after treatment can offer a memorable and suitable period over which the patient can reflect on the treatment impact overall.

Using the WHOQOL instruments also has drawbacks. First, some instruments are quite

lengthy, especially the version 100 items. This will probably not be suitable for cancer patients who are heavily burdened with disease and/or treatment side effects. The short forms are attractive, and our tables show that the WHOQOL-BREF is widely used. Despite its 26 items, the WHOQOL-BREF is more rapid to administer than other measures of the same size as (e.g., the WHOQOL-100) items using the same response scale (e.g., "How much…") are organized together in response scale blocks. Completion is therefore faster than in scales where the response scale changes after every item, as less reading is required. The WHOQOL-BREF is slightly longer than some other instruments, but encompasses a range of domains that are known to be important or very important to QOL assessment. Furthermore, the social relationships and environment domains and a spirituality component are inconsistently included in other assessments [4], but these are likely to be important during cancer. Researchers and clinicians who are primarily interested in a cancer-specific instrument containing symptoms, consequences of cancer, or adverse effects of medical treatment will find seven physical health facets available in the WHOQOL measures: pain and discomfort, energy and fatigue, sleep and rest, mobility, activities of daily living, dependence on medication and/or treatment, and working capacity. If this measure provides insufficient detail, for example, in the physical domain, then the WHOQOL Group acknowledges that a generic instrument like the WHOQOL can and should be co-administered alongside with a specific measure like the EORTC, as together these will maximize comprehension of the breadth and depth of a patient's QOL in the relevant areas. Although the WHOQOL instruments have been psychometrically tested in multiple cancer groups, the WHOQOL instruments are still not often utilized within oncology. As it is quite common practice to administer a large battery of instruments to patients attending oncology clinics, this suggests that the tools that make up the battery should be periodically reviewed and updated, with the aim of updating and streamlining them to two measures – specific (e.g., the EORTC) and generic (e.g., the WHOQOL-BREF) – so that optimally they do the job.

The EORTC QOL group provides information about its instruments on its website. Although the World Health Organization Division of Mental Health only minimally supports WHOQOL instrument users, those who are interested can register to use a particular language version of an instrument by obtaining permission from the principal investigator of the relevant participating center in each country. WHOQOL Group members are listed as authors in the WHOQOL Group's official publications (see references). Potential users of WHOQOL English language measures could contact Dr. Christine Rowland (christine.rowland@manchester.ac.uk) at the University of Manchester, UK, which supports the International Hub for Quality of Life Research.

3.9 Conclusion

The WHOQOL instruments have adequate to good psychometric properties and are suitable to use in the field of oncology, for readers interested in measuring the perceived impact of cancer on life. The WHOQOL instruments can be used in community and public health settings, medical practice, research (e.g., clinical trials, epidemiological studies), to improve communications between patient and professionals in clinical decision-making by feeding-back results. Importantly, the WHOQOL-BREF is already being widely used in service evaluation in other fields, during audit and policymaking. The references in this chapter provide examples of these uses.

3.10 Questions That Can Be Used for Learning/Testing

- QOL is a popular concept. A plethora of instruments have been developed. What are the criteria you can use to determine whether the QOL instrument is adequate for clinical practice or research purposes?

- Is there a need for the development of a WHOQOL add-on specific for cancer, as originally suggested by the WHOQOL Group? Please explain your answer.

Multiple choice item 1
Which of the sample items will *NOT* be present in a WHOQOL instrument?

(a) Are you satisfied with your sleep?
(b) How do you sleep?
(c) How important to you is restful sleep?
(d) *How many hours do you sleep?* [*correct answer*]

Multiple choice item 2
Two hypothetical persons both feel identical pain intensity from a torn ligament in the lumbar spine resulting from a weekend gardening. Both persons complete a health status and quality of life questionnaire. Which statement is correct? Please keep the WHOQOL-group definition of quality of life in mind when answering this question.

(a) *Since both persons feel identical pain intensity, both will probably have similar scores on health status, but different quality of life scores*. [*correct answer*]
(b) Since both persons feel identical pain intensity, both will probably give similar scores on questionnaires assessing health status and quality of life.
(c) Since both persons feel identical pain intensity, both will probably have dissimilar scores on health status, but score similar on quality of life.

3.11 A Topic for Discussion That Can Be Used in Teaching

- Search for a QOL instrument in the field of oncology based on the instrument's name. You can find different generic and disease-specific instruments in, for instance, *Pubmed*. If you think you have selected an instrument, answer the following questions: (i) How did the developers conceptualize QOL? (ii) How did they use this concept when they developed the instrument? (iii) Do the items in the instrument itself sufficiently reflect the conceptual of QOL they described? (iv) Who provided the information about which QOL topics and items should be included (e.g., patients, researchers, clinicians, healthy) and why were they chosen? If you are unable to answer these questions clearly now, then repeat the search, and/or plan your own research project, to fill the gap.

3.12 Further Reading List

This further reading list covers literature about the conceptualization of QOL, selecting a QOL instrument, and development of QOL instrument. In addition, information is provided on the WHOQOL instruments by the World Health Organization.

- Conceptualization of QOL: [10, 97–100].
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  - Skevington SM, Bradshaw J, Saxena S. Selecting national items for the WHOQOL: conceptual and psychometric considerations. Soc Sci Med. 1999;48(4):473–87.
- Selecting a QOL instrument: www.cosmin.nl

- Development of a QOL instrument: www.cosmin.nl
- WHOQOL instruments: www.who.int/tool-kits/WHOQOL

3.13 Research in Context

In 2016, an interesting paper by Llewellyn and Skevington was published in Quality of Life Research about a new methodology, in which the importance scores of QOL aspects can be matched with QOL assessment for each subjective dimension, using graphical feedback [20]. As such, this paper is one of the first studies that shows how the WHOQOL assessments can be used in primary care by to facilitate individualized feedback. In total, 129 participants with and without chronic diseases including cancer learned how to inspect their core QOL scores to identify good QOL. First, they identified aspects of good QoL (high scores), then dimensions where QoL was poor (low scores). Similarly, high importance scores indicated this aspect was very important to them, and low scores less important. Then their attention was drawn to dimensions where there were large gaps between core QoL and importance scores. Of particular interest were those dimensions (facets) where QoL was seen as poor (low score) but important (high). Participants were then invited to consider about how to "close the gap." What sort of things might they consider doing to improve this important aspect of poor QOL? This procedure was guided by the WHOQOL definition which indicates that good QOL results from realizing your *"goals, expectations, and standards,"* that is, those dimensions of life that you see as important. In primary care, discussing QOL results and their importance, for different QOL dimensions, has shown that 65% of the participants report changes to their thoughts and perceptions. Forty percent reported their psychological state had altered, and 34% thought this intervention had changed their planning and expectations for the future. No association was found between self-perceived changes and chronic illness, indicating that the change was independent of health status. Participants were also asked about the importance of sharing QOL information with their health-care professionals. They said that it would be helpful for professionals to have insights into their patient's physical health, psychological state, and lifestyle. Moreover, this study shows that with suitable written guidance, patients can interpret and use this type of QOL information themselves, in the absence of a health professional. This intervention may facilitate self-monitoring and self-management, disease management, and support routine clinical decision-making.

Dedication: From Suzanne Skevington to her husband Nicholas Ferris Britton (1953–2020).

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Developing Cancer Quality of Life Assessment Tools

4

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4.1 Introduction

The importance of ensuring that cancer treatments, interventions and services for people provide the best quality of life (QoL) outcomes for people and populations is well established. QoL assessment is now one of the most widely known and reported patient-reported outcomes (PROs) in cancer care. This has driven the production of a range of assessment tools – referred to as questionnaires, instruments scales or measures – specifically for use in cancer patient populations.

The need and demand for including QoL as an outcome requires robust measurement that can provide scientifically rigorous, clinically meaningful and patient-centred information to inform decision-making. Decision-making can range from individual patient care decisions, the assessment of new health technologies and interventions (including both clinical and cost-effectiveness) through to monitoring the performance of the quality of care including value-based health care across organisations and health care systems [1].

QoL demands the same attention to its quality as any other outcome measure used to inform health care decisions, particularly where the focus is on capturing outcomes from the perspective of patients. Within the context of a cancer trial, if QoL is included as an endpoint of concern, the findings drawn from measuring QoL can be critical to the trial conclusions [2], so similar scrutiny of any bias and error is required. The reliability and validity of the assessment tool used is a critical determinant. Therefore, the development of a cancer QoL assessment tool must be undertaken in a robust, systematic way.

This chapter enables the reader to: (a) understand the basic foundations to and key principles in developing a QoL assessment tool; (b) apply this understanding to the research process involved in developing a QoL assessment tool; (c) consider other issues in the development of a QoL assessment tool, with signposting to other chapters and literature for further reading on related topics.

There are three key stages in the research process to develop QoL assessment tools. These are stage (1) getting started – setting out the rationale and proposal for the development process; stage (2) development; and stage (3) validation. This chapter primarily focuses on stage 1 and 2. More information on validation can be found in Chap. 7.

4.2 The Basic Foundations to Developing QoL Assessment Tools

The development of QoL assessment tools must be made on strong theoretical and conceptual foundations including placing current QoL assessment in the context of the growing international interest and efforts in PRO measurement.

4.2.1 Conceptual Basis of QoL Assessment

Alongside a robust measurement strategy, the conceptual basis (or framework) for QoL is the one of the key foundations to put in place prior to developing a QoL assessment tool. The consequences of not having a sound conceptual framework can include selecting the wrong measurement strategy and choice of tests in validating the tool. It can lead to a lack of sufficient

evidence on its development and poor performance of the tool, wasting considerable resources, causing harm by making wrong conclusions – from a purported patient perspective – and/ or rejection of the QoL claims by regulatory bodies [3].

A conceptual framework helps to explain the construct of QoL underpinning the tool, intended scales and the relationships between items, that is, supports the measurement strategy adopted and the interpretation of data captured by the QoL assessment tool. Whilst an in-depth account of the debates and positions on defining QoL is beyond the scope of this chapter (Chap. 1 considers these arguments), it is important to be clear from the outset what is meant (and importantly what is not meant) by the definition of QoL guiding the development of the assessment tool.

QoL within the context of health is generally considered as a subjective and multi-dimensional concept at an individual level [4]. Within health, QoL has often been conceptualised, for example, into health-related QoL – sometimes also regarded as disease-specific or condition-specific QoL [5]. Generally, health-related QoL is concerned with those aspects of a person's life that have been directly affected by their health. Within cancer, this would be to consider the health-related impact of cancer. Typically, domains such as disease symptoms, treatment side effects, functional status (e.g. impact on physical, social and psychological functioning) and general health/QoL may be domains of interest in capturing cancer-related QoL [6]. A broader concept of QoL would capture aspects of a person's life that go beyond health, for example, well-being or satisfaction [4]. Individual QoL has been considered under a different conceptual basis as part of the WHO approach to QoL assessment, although this assessment approach considers generic QoL rather than cancer-specific QoL assessment [7]. As summarised in Chap. 2, in cancer there has been an explicit move from earlier 'clinician-rated' measurement of health status to assessment tools which consider aspects of QoL from the perspective and self-report from the patient. For the purposes of this chapter, the focus is on assessment tools which measure health-related QoL as a result of cancer and its treatment. Whilst this chapter will continue with QoL as a 'shorthand' term, it is focused on developing an assessment tool which cover assessment of health-related QoL domains/concepts of importance and relevance to different cancer patient populations.

4.2.2 Patient-Reported Outcomes

The considerable attention to PRO measurement in recent decades has been transformational in the application of PRO measurement (e.g. as QoL) in cancer research, policy and practice. Cancer-specific QoL assessment tool can be generally regarded as a PRO measure. The definition of a PRO by the FDA [8] is often cited (Box 4.1) in framing the commonalities of outcomes (e.g. QoL, satisfaction with care). Consideration of QoL assessment under the umbrella of PROs has enabled QoL to be harmonised with the considerable efforts to develop, use and interpret PRO information.

Box 4.1: Definition of a

A PRO is any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else. The outcome can be measured in absolute terms (e.g., severity of a symptom, sign, or state of a disease) or as a change from a previous measure. In clinical trials, a PRO instrument can be used to measure the effect of a medical intervention on one or more concepts (i.e., the thing being measured, such as a symptom or group of symptoms, effects on a particular function or group of functions, or a group of symptoms or functions shown to measure the severity of a health condition) [8].

4.2.3 Measurement Theory

The development of QoL assessment tools must be underpinned with understanding of measurement theory [9]. This is often captured under the term 'psychometrics', but 'clinimetrics' is also a term used in relation to health measurement. Whilst there is debate about which term is more appropriate, there is much overlap, with Streiner stating that clinimetrics is a sub-set of psychometrics [10]. For the purposes of providing a simple overview, the focus will be on briefly summarising the main theories and the measurement properties that underpin validation. An in-depth account on the properties that underpin the validation of QoL assessment tools is presented in Chap. 7, with application of modern measurement approaches the subject of Chaps. 8 and 9.

The traditional (standard) approach has been to use classical test theory methods to develop standardised tools. Tools are usually made up of scales, which can be multi- or single item. A scale, which is a latent variable, reflects the construct of interest, for example, physical functioning, and is made up of items that tap into it, for example, ability to take a short walk [9]. In simple terms, the items being measured are indicators of the underlying construct. Item response theory (IRT) and RASCH measurement theory are two other psychometric measurement theories that can be used (sometimes referred to as modern measurement approaches). All three approaches have different strengths and limitations [11–13]. In early development stages, some common steps are shared between the three approaches (e.g. in generating QoL issues). However, it is important to select the measurement strategy carefully as it will underpin the design and subsequent testing (validation) of the assessment tool. In the development process, establishing the *content validity* of the assessment tool is essential. It is probably the most important aspect of measurement as this underpins the validity of the assessment tool. This is discussed later as part of the first stage of developing a QoL assessment tool.

In addition, other challenges to consider from the outset may depend on the specific populations – such as undertaking QoL assessment in very young children, people with significant cognitive impairment or where health literacy may preclude standard ways of collecting PROs. In such circumstances, further investigation may be needed, for example, use of proxy assessment [14]. Chapter 19 considers proxy assessment in depth.

Spending time developing a comprehensive understanding of the conceptual basis of QoL (including PROs) and measurement theory alongside early consideration of some of the specific challenges in the cancer population of interest is a necessary investment in ensuring that the development process is based on strong footings.

4.3 The Process of Developing QoL Assessment Tools

The growth in demand for standardised, robust QoL assessment in cancer has gathered considerable pace in recent decades, although the attention to robust design has been at the cornerstone of long-standing and well-recognised international activities in this field for several decades. Much effort has been undertaken to produce evidence syntheses, compendiums and databases to capture and distil information on the plethora of assessment tools available for use in different cancer populations and settings. Alongside, this, there have been coordinated activities to harmonise and enhance the reporting, the quality appraisal and selection of PROs. The COSMIN initiative [15] provides guidance on how to choose the most suitable outcome measure. The attention and critique of how such measures are developed is a substantial component of COSMIN, and referring to the COSMIN checklist can aid the understanding of what are the key components of a good quality tool.

Within cancer, there are published guidelines to develop QoL assessment [16], and these provide an excellent basis to developing QoL assessment tools. Chapters 5 and 6 are devoted to the EORTC and FACIT measurement systems for QoL assessment: both used widely across the world. ISPOR (The Professional Society for

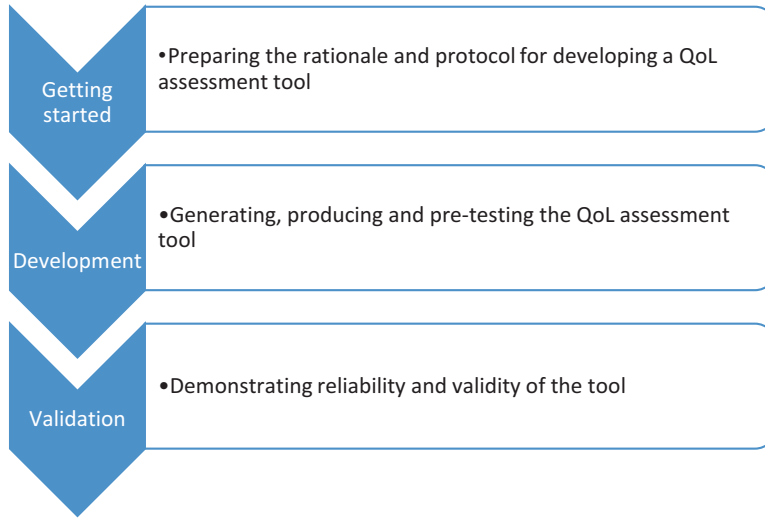

Fig. 4.1 The three key stages of QoL tool development

Health Economics and Outcome Research) have produced a range of good practice guidelines for PRO development. For development, the good practice guides on concept elicitation [17] and assessing respondent understanding [18] provide a comprehensive overview of key steps involved. For this chapter, the basic elements and steps in the research process will be considered in developing a QoL assessment tool, organised into three key parts (Fig. 4.1).

Underpinning these three stages are the collaborations and partnerships which are crucial to the development of QoL assessment tools. The development of QoL assessment is a complex and resource-intensive activity, often requiring dedicated researcher time and effort over (what can be) several years from first idea to publishing the final 'validation' of the developed tool. Alongside the empirical and theoretical knowledge required, the experiential knowledge gained from participating in and leading the development of QoL assessment tools has helped to build capability and capacity in this area of cancer-related QoL research.

One of the successes of well-established instrument development is that it has involved multi-disciplinary teams, frequently across many countries. These teams often draw upon extensive clinical networks and patient networks to ensure that the final, validated QoL assessment tool has significance and reach to justify the investment made in the development process. QoL developers come from a variety of backgrounds such as medicine, psychology, nursing and statistics, and this diversity has been a strength to the field. Developing QoL assessment tools demands understanding of psychometrics and PRO measure design, experience of qualitative and quantitative research methodologies and understanding of the intended population, as well as excellent project management and communication skills to coordinate (often) multi-site studies.

In addition to healthcare professionals and academics, the central role played by patients in the development of QOL tools is now being recognised and added to guidelines to ensure patients are fully involved and engaged from the outset. Patient involvement should go beyond 'patients as participants of research': they should be supported and encouraged to contribute to every aspect of the study, including the design and conduct of the research. Patients may choose to contribute in a variety of ways, for example, as a member of a patient panels through to being full co-investigators or researcher, with different levels of commitment and support required. As patients are recognised as key stakeholders in the international regulatory and health policy community [19], attention has correspondingly been raised on how to fully incorporate patient involvement throughout the development process of

Box 4.2: Practical Considerations for Patients (and Public)

National and/or local guidance should be consulted on how to include patients (and public) in research. Clear definitions should be consulted to guide the role and contribution of patients in the research process.

Where possible, expertise in involving people and patients in research should be accessed as part of establishing the development team.

Patient involvement should be clearly articulated in the research proposal. Where a patient is a formal member of the research team (e.g. co-investigator), they should be part of the development process as early as possible.

A description of the role the patient representative(s) would be expected to have in the research process should be clearly outlined in accessible language. The recruitment process should be considered carefully, for example, whether recruitment will be from local clinics/settings or from national patient groups.

Consideration should be made to ensure patients can be fully involved in the research such as time, location and format of meetings. Training should also be considered.

Consideration of the time and costs for patient involvement should be fully considered during the development process and funding support to reimburse patients (e.g. for travel expenses).

PROs [20]. Some practical considerations to incorporate patient involvement into the development process are suggested (Box 4.2).

The development of QoL assessment tools provides several key opportunities to fully embed patient as partners in the research process with some agreement of where this can be optimised [21]. An important first stage in assessing whether or not a new QoL assessment tool is required, is to involve patients in setting out what areas of QoL assessment should be captured, for example, for a new therapy, whether capturing treatment side effects is of most concern or whether psychosocial aspects should be captured. Designing the patient information forms with patients is often required by ethics committees and developing the interview schedules (including piloting) with patient representatives ensure that these can capture the voice and perspective of patients in generating QoL issues which matter most for them. Once items are generated and the QoL assessment tool begins construction, involving patients in assessing whether the tool is comprehensive and can be completed is vital alongside ensuring that the production of the final QoL assessment tool is fit for purpose from the patient's viewpoint before validation. The framework by Carlton et al. [20] is a useful starting point in exploring how patient involvement can be included.

4.3.1 Stage 1: Getting Started

4.3.1.1 Rationale for Developing a QoL Assessment Tool

A vital first step for developing any new QoL assessment tool is to create a compelling, evidence-based rationale [22]. Ensuring that there is a need and demand for a QoL assessment tool is critical before investing in what can be a long, complex and resource-intensive development journey. This is usually (and should be) essential in obtaining research funding or seeking endorsement (if relevant) if working with a research group or clinical network.

Careful, expert peer-reviewed scrutiny should ideally be given to the case for developing a new tool. This ensures that the tool is sufficiently distinctive and original (i.e. does not unnecessarily replicate what is already available or replicate the limitations of existing tools) and the basic foundations for the development have been carefully thought through in advance.

Undertaking a review of the current evidence for assessing QoL in the cancer population of interest is a necessary part of creating the case for

why a new assessment tool is required. The review should (1) scope the current evidence-base for QoL assessment in the cancer population; (2) present the rationale for the need/demand for a new QoL assessment tool in this area, such as the introduction of new therapies with new symptoms/side effects and (3) produce a clear definition of the purpose of the assessment tool, the domains it will potentially measure (e.g. representing health-related QoL) and the population/setting that the assessment tool is intended for. Depending on the destination of the review (e.g. as part of a funding application, PhD proposal or published work), the size and scope of the review may differ. It could be a scoping, structured or full systematic review [16].

4.3.1.2 Feasibility

As well as providing a coherent rationale for developing a new QoL assessment, it is important to demonstrate that it is also feasible. For example, the patient pool for rarer cancers will, by definition, be smaller than more common cancers. It is important to consider whether there will be enough patients who can contribute to the development in the time available. Alternative approaches and strategies may need to be considered for rarer cancers.

4.3.1.3 Defining the Population of Interest and Scope of the Assessment Tool

There are several basic elements required in order to set out the purpose, form and function of the assessment tool [22]. The underlying conceptual basis for the assessment tool should be well thought out. For example, if the assessment tool is intended to measure health-related QoL, a definition and framework of what domains (concepts) the module will cover should be presented. In addition, the measurement approach to the assessment tool should also be considered as part of developing the protocol for the development work. Whilst this chapter concentrates on the development of QoL assessment tools for use primarily in cancer clinical trials and studies, the intended use of the assessment tool (e.g. for monitoring the performance of healthcare or facilitating patient and clinical decision-making in daily practice) should be clearly specified.

It is very important to define the intended population for the tool as this will enhance the ability of the assessment tool to capture the key QoL issues for that population, that is, precision. This chapter has focused on the development of cancer-specific tools rather than general measures (which capture issues across different health conditions). Disease (condition)-specific measures enable the capture of the most relevant, important and meaningful issues. This enhances the sensitivity/specificity of the measure to identify changes in health-related QoL over time, for example, as a patient goes through chemotherapy, and/or between groups, for example, to compare the QoL impact of different therapies. Further information on generic versus disease-specific measures is described in Chap. 3.

When defining the population of interest, any sub-populations or treatment groups also need to be taken into account. With the changing cancer landscape, QoL assessment tools need to reflect a diverse cancer pathway such as active treatment, rehabilitation, survivorship and palliation. Careful consideration is required to make the decision on whether to develop separate tools for sub-populations and treatment groups or whether to focus on the issues common to all. Examples of the former approach include the development of a metastatic breast cancer instrument [23] (because the treatment profile and QoL impact is different compared to early-stage breast cancer) and an instrument specifically for older people [24] (because of the unique concerns and priorities of this group).

In defining the intended population, there should be a careful balance between precision and comparability. This should be considered at the earliest stage and in collaboration with patients and clinical experts in setting out a clear research question for the development process. The limitation of disease-specific measures is that they can preclude evaluation across different cancer populations or studies, if there is heterogeneity in the choice of measures used. In addition, there are

particular challenges, such as patient recruitment, when developing assessment tools in rarer cancer patient populations. With growing advancement in the genetics of cancer and availability of more targeted therapies, QoL assessment tools may need to adapt to this changing landscape [25].

4.3.1.4 Development of the Research Protocol

It is imperative the process of developing a QoL assessment tool is first set out in a detailed research protocol. This is often mandatory as part of obtaining required funding, governance and ethical permissions. Whilst the content, order and format of the protocol may differ for each project (and will often be subject to specific requirements such as the funder, ethical committee or research group), a basic framework (Table 4.1) can help guide the design. At different stages of the development process, a specific protocol (e.g. to guide a systematic review), or more detailed statistical analysis plan (e.g. if preliminary psychometric testing is conducted during the pretesting stage) may be required.

4.3.2 Stage 2: Development

The development process is primarily concerned with establishing content validity. Content validity is the basis for establishing measurement validity. If tools are designed to measure QoL-related aspects of cancer, the tool must ensure it is measuring the concepts or domains of interest related to the cancer population of interest. In psychometrics, this ensures that the items within the measurement tool represent and relate to the construct being measured. Whilst face validity can give a quick judgement on whether the tool appears to 'on the face of it' be reasonably capturing the domains and items of interest, establishing content validity requires formal attention. In practice, this requires attention to both the content and structure of the assessment tool, including assessing whether patients can understand and complete the questions. Generating evidence of these core attributes must begin at the start of any QoL assessment tool development.

Whilst all standard texts and papers on psychometrics will cover content validity, there has been criticism that despite its importance, it has been largely overlooked in terms of its methods – termed validity by assumption, simply because a few experts have looked at it and said so [22] or it has not been sufficiently documented. However, there is recognition that content validity is a necessary attribute that must be derived through comprehensive and robust methods in order to inform decision-making. For example, the FDA guidance on PRO measurement gives an explicit definition of content validity as '… *defined by the empiric evidence that demonstrates the items and domains of an instrument are appropriate and comprehensive relative to its intended measurement concept, population, and use*' [8].

In deriving the issues for inclusion in a QoL assessment, the activities discussed in part 1 are critical sources to begin with: setting out the context for the assessment tool (i.e. population of interest) and intended scope of use (e.g. for specific treatment or diagnoses) alongside the proposed conceptual and methodological framework for content validity. With regard to methodological framework, the use of qualitative methodologies is now established in playing a central role in both generating issues for inclusion (concept elicitation) [17] and in assessing respondent understanding [18].

A range of qualitative research theoretical approaches and methodologies are proposed – including phenomenology, grounded theory and thematic approaches. A detailed synopsis of the strengths and limitations of each potential approach is beyond the scope of this chapter, and further reading may be necessary, for example, [27, 28]. However, in choosing the approach for the assessment tool development, careful scrutiny is required to ensure there is consistency and coherency with the theoretical and conceptual basis as well as conducting a rigorous research process through the data collection and analysis procedures. One of the challenges is enabling the development process to be informed by previous knowledge (e.g. through the production of a proposed conceptual basis, expert views and the literature) whilst also being responsive and

Table 4.1 Suggested outline of key sections in a research protocol for developing a QoL assessment tool

Heading	What information should be provided?
Title	A succinct overview of the purpose, population and design of the development process
Background and literature review	Rationale for the QoL assessment tool and critical summary of the evidence base including methodological limitations in current assessment approaches. The conceptual and theoretical basis to the development should be provided
Intended population	A clear description of the intended population (e.g. diagnoses/treatments) to be covered by the assessment and setting (e.g. clinical trials)
Research aims and objectives	Well-defined aims and objectives to set out the overall purpose of the development process
Methods	A clear plan of investigation, where applicable based on established development guidelines/methods
Sample and sampling approach	Each stage/phase should include appropriate sampling methods to obtain a representative sample of the target population and sample size considerations should be included. If the QoL assessment is intended to have an international focus, there should be a clear account of how this will be incorporated throughout the development process
	The approach taken to access and recruit participants at each stage/phase should be clearly presented in line with ethical and governance requirements
Ethical and governance	Ethical and research governance permissions should be accounted for, including any data sharing permissions required. A data management plan may be required
Phase1a: Generation of QoL items (literature review)	The review process should be summarised and where applicable, follow established guidelines, for example, PRISMA [26]. A separate protocol may be needed
Phase1b: Healthcare professional interviews	As above, the data collection and analysis of healthcare professional interview should be clearly described
Phase1b: Patient interviews	The data collection methods and analysis of patient interviews (e.g. qualitative research approach used) should be clearly described, following guidance in ensuring content validity of QoL items
Phase 1c: Generating the list of QoL issues	The process of generating a provisional list of QoL issues should be summarised, including the decision rules used to select the list to develop into a provisional tool
Phase 2: Constructing a provisional QoL tool	The overview of constructing the QoL tool should be given, including the rationale for the time-frame, format and wording. How QoL issues will be constructed into items and provisional scales should be detailed. If applicable, the approach to translation at this stage or the use of item libraries/other questionnaires to inform item construction should be documented
Phase 3: Pre-testing the QoL assessment tool	The method of data collection and analysis of the pre-testing stage (to identify and solve issues in its administration, e.g. poor wording of items) should be specified. If applicable, any preliminary psychometric evaluation should be explicitly described
Outputs	The output of the development process should be provided, including plans for validation of the QoL assessment tool. This could include intended reports or papers for submission. A dissemination strategy can provide an account of how the development process will be communicated to key stakeholders and wider academic/non-academic audiences
Expertise of the research team	The name and roles of the research team and their specific contribution to the research should be summarised. This should include patient (and public) involvement in the research process
Study management and coordination	The project management and coordination of the development process should be provided, including quality assurance checks throughout
Study timetable	The key milestones and timetable (e.g. in a Gantt chart format) should be presented and can then be used to track progress

reflective of enabling the generation of QoL issues to be informed from the experiences and perspectives of patients, ensuring that this facilitates new understanding of what QoL may mean for these patients. This move between deductive and inductive approaches is reported as crucial in developing sensitive and comprehensive PRO measures [17].

Although different terms can be used to describe the individual steps during the development process, the term 'phase' will be used, similar to the steps outlined in recognised guidelines for developing QoL tools in cancer [16].

4.3.2.1 Phase 1: Generating the QoL Issues

Three key steps are taken: (1) literature review, (2) interviews with professionals (3) Interviews with patients. *The core group in capturing QoL concerns and establishing content validity are patients*. Whilst these are presented as a consecutive series of steps, in practice these are often done concurrently as part of attending to the development of a sensitive and comprehensive tool. The sequence may also be influenced by the chosen methodology, particularly for patient interviews. For example, if 'pure' qualitative methodology is used then a literature review is often done alongside or after data collection to minimise bias and to support the analysis and integration of qualitative data.

Phase 1a: The Literature Review

Whilst there is no formal requirement, literature reviews often take the form of a systematic review, following established principles to searching and selection of the evidence. Even if a formal systematic review is not undertaken, there should be at least be a documented process to how the evidence was searched and selected for review. A review protocol can ensure that the design of the review addresses the questions that need to be addressed. Typically, these questions will focus on:

1. What QoL instruments are currently used in the population of interest?
2. What are the strengths and limitations of current assessment tools?
3. What are the QoL concerns/issues for patients (in the population of interest) identified in other studies?

Such broad questions should be appropriately refined and reviewed before designing and conducting the search process. A number of relevant databases may need to be selected as QoL assessments are reported across a wide range of academic journals and reports. This also means several key terms, for example, QoL, HRQOL, PRO, should be used in the search. In addition, where assessments are focused on treatment related issues, reviewing clinical information in the reported toxicities/side effects may also be a useful information source.

Undertaking a scoping review first and accessing the expertise of information specialists can help produce a search strategy with sufficient sensitivity and specificity. A broad range of evidence sources may be needed (including quantitative, qualitative and mixed methods study). For example, whilst questions 1 and 2 above may focused on 'measurement', question 3 may require in-depth assessment of qualitative studies which have explored QoL-related experiences from the perspectives of people with cancer.

For questions 1 and 2, a structured appraisal can be undertaken. This can use frameworks that have been utilised in previous review of QoL assessment in cancer, for example, [29], and other guidance such as the COSMIN checklist [30, 31]. For question 3, the review can use other checklists (e.g. CASP) [32] relevant to the study method employed. Depending on the evidence found, qualitative synthesis may enable the generation of QoL issues from the descriptions and accounts reported in the literature.

Phase 1b: Interviews with Professionals

Interviews with professionals are an important but not sufficient step on their own in generating QoL issues. The same methods could be employed as patient interviews, particularly if the intention is to explore perspectives (and possible differences) as part of an in-depth qualitative

study including refining the conceptual framework for assessing QoL in the chosen population [33]. However, this may need to be balanced with the aim of capturing professional perspectives alongside the practicalities of time and opportunities associated with competing demands on busy day-day roles.

In sampling professionals, a sampling plan and approach should reflect a diverse, multidisciplinary context of professionals (e.g. oncologists, surgeons, radiologists, specialist nurses, clinical psychologists) that would be involved in the care of the chosen population, alongside sufficient expertise and experience. An international sample would be important to reflect possible variations in care in different health organisations and systems. A sampling framework can facilitate recruitment.

Professional interviews can provide opportunity for the provisional list of QoL issues generated from the literature to be reviewed for content and identify any missing issues. It can also elicit views on what are the most relevant (or irrelevant) issues to be included in an assessment of QoL and what are the most important issues of concern. If appropriate, this can also be done using an established QoL assessment tool. Again, an appropriate interview guide and analysis approach should be produced in the protocol.

Phase 1b: Interviews with Patients

As stated previously, qualitative research methodologies can facilitate generating QoL issues – often referred to as concept elicitation [17]. At the heart of this should be capturing the experiences and perspectives of patients who represent the target population. This should not just capture clinical characteristics but also take into account any demographic (e.g. age, gender, education), geography (e.g. secondary care, ambulatory setting) and language/culture (e.g. where the tool has an international focus). A sampling approach should reflect the intentions of capturing a broad representation, for example, purposive sampling, and a sampling framework can help guide the recruitment of patients in specific categories to achieve balance across the population spectrum and avoid potential biases in recruiting from a small selection of patients (e.g. sampled from only one treatment group of interest). Whilst sample size considerations should be made in line with the chosen methodology, 'data saturation' is often a guiding principle, for example, interviews should cease when no new issues are generated from interviews. Careful consideration should be placed on obtaining a diverse patient sample and quality of the interviews that reflect the intended population rather than 'numbers' of patients [8].

The design of the interview approach should be commensurate with the employed methodology. Typically, open-ended interviews or at least semi-structured interviews (rather than structured interviews) are advocated, and careful attention should be given to their development and piloting. Here, patient involvement in the research process can be valuable in designing the qualitative protocol. Focus group or individual interviews can be undertaken: both methods have pros and cons [17]. For example, whilst individual interviews enable in-depth exploration and probing of topics of relevance and importance to that patient, these can be time-consuming, and it can be difficult to compare complex information across the whole patient cohort interviewed. Focus groups are more time efficient and can allow experiences to be compared in real time, but there is the risk that one or two 'views' within the group will dominate. For all interview approaches (including mode, e.g. face to face or virtual), training and practice in interview techniques should be a pre-requisite before main data collection.

The analysis approach should follow the methodology described in the protocol. In addition, it is vital that an auditable decision trail is made to provide a transparent account of how the qualitative data (e.g. verbatim transcripts) are managed, the steps undertaken to extract data (typically as codes) and how these are assimilated into categories which represent patient perspectives and accounts of their QoL experiences. This can be guided by the conceptual framework although in the inductive approach, the original framework can be refined to reflect emerging categories and support the grouping of QoL issues

into potential concepts/domains. Items should have a clear description, using patient words and 'thick' description from patient accounts (e.g. supporting quotes). Appropriate mechanisms for assessing the rigour of the analysis should be undertaken. This may involve respondent validation of emerging categories and themes with patients and/or independent coding and comparison between researchers.

As part of the interview process, an established assessment tool can be shown to help elicit new issues from the patient's perspective, to assess whether further issues are not covered or as a prompt to ask patients which issues should definitely be included (or excluded) in an assessment of QoL. However, this is an additional step and should not form the basis or be the primary purpose of interviews to ensure the content validity of the instrument.

Phase 1c: Generating a List of QoL Issues

The processes in stage 1 may result in a lengthy list of issues. Through analysis, careful attention to coding and categorizing information, potentially duplicated issues can be 'collapsed' or combined to reflect patient account (e.g. in describing back pain, key examples could be used rather than writing separate questions for each location). It can also be useful to compare the QoL issues generated from the patient interviews with the literature and healthcare professional interviews to rule out issues that were not evident in the patient accounts. However, removing any issues generated by patients should be avoided until further consultation. The output from stage 1 should be an exhaustive list underpinned by in-depth evidence of the QoL concepts/domains (and corresponding issues) for the intended population, which can also form the basis of a revised conceptual framework that underpins the QoL assessment tool.

4.3.2.2 Phase 2: Constructing the Pilot (Provisional) QoL Assessment Tool

Constructing the QoL assessment tool involves two complementary tasks. The first task is devising items from the QoL issue list generated in phase 1. Depending on the length of the list, refinement may be needed; however, it is important that items are not omitted at this stage without clear decision criteria and an auditable account of this process in order to minimise selection bias. If such decisions are needed, then there should be explicit consultation with a new representative sample of patients (and professionals).

The task of transforming the exhaustive list of QoL issues into a provisional (draft) assessment tool often requires several iterations and expert review, involving patients, professionals and experts in designing QoL assessment tools. Translation specialists may also be valuable, if relevant, to identify potential translation issues at an early stage. The major methodological considerations required for item construction are considered in standard textbooks on health measurement [9] and are also reflected in good practice guidelines [18]. Overlap with other QoL assessment tools should be examined to demonstrate why a new QoL assessment tool is required (e.g. the QoL issues generated are not sufficiently covered by established tools). However, to avoid breaking copyright law, caution should be applied to copying from other QoL assessment tools without permission, and in all cases, where an item is extracted from another tool, permission should be obtained and the source acknowledged.

Databases such as PROQOLID™ [34] can be useful sources to identify and review existing tools. The emergence of Item Libraries has also created a repository of items, which can be used in particular circumstances. This can include where an existing tool can be supplemented with additional items (or scales) rather than developing an entirely new tool or where a QoL tool is being developed following specific guidelines. The guidelines for the use of specific item banks should be consulted (e.g. EORTC) [35] and Chap. 5 discusses this item library and its role in QoL assessment development.

The second task is to construct the items into scales and where necessary single items, taking into account the scaling response (e.g. use of Likert scales), the time-frame (e.g. whether the

respondent is asked to recall over the same day, week or month), structure of the items (e.g. as statements or questions) and organisation of the tool (e.g. similar items of proposed scales grouped together). Ensuring the tool can be easily read, understood and completed by a patient without unnecessary burden are crucial considerations in this process.

Wide consultation on the provisional item list and draft tool is essential for the development of a high-quality tool. This should include patients from the target population and professionals (who were not involved in stage 1) alongside clinical and methodological experts in QoL assessment.

By the end of stage 2, a provisional version of the tool will be ready for pre-testing in stage 3. This version is likely to contain more items than the final version of the tool, but if enough careful work has gone into stage 2, there should be relatively few, minor changes to make to the wording of items in the next stage.

4.3.2.3 Phase 3: Pre-testing the QoL Assessment Tool

In phase 3, patient (respondent) understanding of the provisional QoL assessment tool is evaluated first. If the QoL assessment tool is poorly constructed, through badly worded items for example, or it is difficult to complete, there will be an increased risk of missing data when used and its utility as a PRO measure will be severely limited. The psychometric properties of the tool may also be impacted, for example, the way a question is written could result in poor discrimination and limited evidence of construct validity. Asking questions which tap into exactly the same thing or very different concepts could impact on the scale structure.

As with all stages, the development protocol should carefully document phase 3 methods and good practice guides and guidelines should be accessed to support this. To ensure the full spectrum of the intended population for the QoL instrument is captured, the target sample should be derived using a similar approach as the stage 1 patient interviews. However, patients who took part in stage 1 should not usually be invited to take part in stage 3. Again, sample size should be guided by the principle of quality rather than quantity, but established guidelines suggest a general rule of approximately 15 patients in each of the specific treatment groups/diagnoses stages across the intended population to enable balance.

The methods for assessing patient responses and analysis should be planned. This will include pre-determined decision rules on which items should be retained or excluded and whether newly suggested items can be included in the QoL assessment tool. Rules could be based on patient ratings of importance/relevance, mean and range of scores, evidence of potential floor/ceiling effects (e.g. responses are skewed to the highest/lowest response category) alongside qualitative responses. ISQOL guidance [18] recommends a final tracking matrix to provide an auditable and transparent account of the destination of each item in the assessment tool – from initial conceptualisation in stage 1 patient interviews through to its ultimate inclusion or exclusion in the QoL assessment tool. In practical terms, a MS Excel® spreadsheet or MS Word® document can be used and should be made available ideally publicly in a paper or report or on request.

Cognitive interviews are recommended to assess the comprehension of each question/item and to evaluate whether any item is problematic in terms of its wording or phrasing. Typically, cognitive interviews include the use of 'think aloud' methods and/or verbal probing [18]. These are quite separate interview techniques (for researcher and patient) from standard approaches and so researcher training may be necessary prior to undertaking interviews. 'Think aloud' [18] involves the patient completing the assessment tool in the presence of the researcher, and verbalising out loud their thoughts and responses as they read and respond to each item. Verbal probing by the interviewer can be used to ask the patient to say what they think the question is about. Throughout, the interviewer should not be guiding the patient but if guidance is required, this should be taken into consideration when the tool is revised. Cognitive interview approaches derived from other contexts and methods and fur-

ther consultation on the literature devoted to cognitive intervening and PRO development are recommended [36, 37].

On completing the questions, a general debrief can be undertaken to ask the patient to reflect on the tool as a whole in order to identify other issues such as duplicated questions, whether the format of the tool is appropriate and whether the time-frame is appropriate. Other considerations such as the length of time to complete the tool can also be gathered and patients can be invited to propose additional items.

In addition to commenting on the content and format of the questionnaire, patients may also be asked to score the importance and relevance of items, either for each item individually or by picking out the most important and relevant items. These data can contribute to the decision rules about which items to retain and which to exclude.

From the results of the respondent understanding, the QoL assessment tool can be revised including proposing a hypothetical scale structure. This often requires further consultation with patient and professional representatives.

Before validation, it is advisable to carry out some preliminary evaluation of the psychometric properties of the QoL assessment tool so that it is the final version of the measure which is used in the validation study. The psychometric analyses in this part are exploratory, whereas the Part 3 analyses should be confirmatory. The sample size required for the preliminary evaluation will depend on the complexity of the tool, as defined by the number of items, the number of scales, the number of items per scale, the homogeneity within scales and the homogeneity of the patient sample, but it will typically involve 100–300 participants. Patients can simply be asked to complete the QoL assessment tool so the burden of participation is low. Internal reliability of the hypothesised scales can be evaluated using Cronbach's alpha coefficient, correlation-based methods and exploratory factor analysis (see also Chap. 7, this volume).

The development process should result in the production of a QoL assessment tool with evidence of its content validity, that its structure and format is applicable for use in the intended population and some preliminary psychometric evaluation to support the proposed scale structure. The tool should also demonstrate coherency with a sound conceptual and theoretical basis in place. Any development process which has followed specific guidelines should also result in evidence to demonstrate adherence to these guidelines in accordance to the funding body or group.

4.3.3 Stage 3: Moving from Development to Validation

A robust development process is one part of the key evidence required to demonstrate the quality of a new tool. The other key part is validation. At this stage, the assessment tool should be sufficiently robust that the focus can be on formal and final validation. Chapter 7 considers the process of validating QoL assessment tools which is the third stage of developing QoL assessment tool.

Ultimately, if rigorous attention has been paid to the development, the QoL assessment tool should require little or no minor modification to its content and structure following validation. If substantive changes are necessary, for example, several items or a scale require revision, this could render the validation itself 'invalid', and there may be a need to conduct a second validation study, which could result in considerable delay, time and resources to repeat a large-scale study. These potential consequences demonstrate the importance to spend time and effort on the development stages.

In some cases, validation may be able to 'piggy-back' on a study using the provisional version of the tool. For example, it may be possible to use a provisional tool, with the explicit caveat that formal validation has yet to be done, in a phase II clinical trial or observational study (although not in a phase III trial, particularly if part of a regulatory claim, when evidence of reliability and validity will be required). This can help generate evidence of its psychometric performance in a different context, and it may enable the concurrent design and conduct of a validation

exercise. However, the same metrics as provided in a standalone validation study would still be required.

In addition to evidencing validation, the validation study can also provide data to support the later use and interpretation of the new tool. For example, the minimally important (clinical) differences (MIDs), which are important from both a patient and clinical perspective, of each scale could be identified. This is described in more detail in discussing the statistical considerations in analysing QoL data (see also Chap. 10, this volume).

4.4 Additional Considerations

Some additional considerations are briefly considered in relation to their application in the development process below, with further signposting to relevant chapters.

4.4.1 Translating Cancer QoL Assessment Tools

An important area of consideration from the outset of development is whether the instrument is intended for use across different countries, languages and cultures. This allows QoL data to be aggregated across populations. If a QoL assessment tool is used in a different language than the original language the tool was developed in, then it must go through a rigorous translation process. Linguistic equivalence evaluates whether the translated QoL assessment has semantic equivalence with the original tool (i.e. the QoL items still have similar meaning between languages) [38]. A broader consideration is cross-cultural applicability [5]. Cross-cultural considerations are considered in-depth in Chap. 13.

There are two main approaches in developing international QoL assessment tools for cancer. First, development of QoL assessment tools can be co-ordinated with an international focus from the outset. An example would be the EORTC QOL Group guidelines for QoL instrument development [16] which follows rigorous translation procedures throughout the development process [39]. An additional (or alternative) step is to undertake subsequent studies once the QoL instrument is translated and validated within a particular language or country. International groups [40], have published methodologies for the translation and establishment of linguistic equivalence.

The basic framework to incorporate translations into the development process is based on a forwards-backwards translation process. This requires additional fieldwork. This typically involves forwards translation of the original language version by two translators who are native speakers of the language to be translated into and fluent in the original language. The translated version is then reconciled by a third translator. The agreed version is then backwards translated into the core language by translators with appropriate fluency in both languages and again, with reconciliation. The process is then reviewed by experts including independent proof reading with a consensus reached. The instrument can then be piloted in a representative group of patients who reflect the target population for the instrument (e.g. cancer diagnosis, educational status, age). A structured interview (either individual interview such as a cognitive debriefing interview or focus group) will then assess whether the translation assessment tool and its items is understandable for patients. Following review, a final translated version is agreed and can be used in this population, including in the piloting and validation of the QoL assessment tool. In considering developing QoL assessment tools for use within an international context, the investment of time, resources and expertise for high-quality translations following international good practice must be factored into development.

4.4.2 Adapting, Updating or Combining Existing QoL Assessment Tools

There have been tremendous advances in cancer treatments over recent years, including the advent of new therapeutic options such as immunother-

apy, biological and targeted therapies. In addition, new radiotherapy, radiological, surgical and supportive care interventions can be offered alongside increased attention to the longer-term impact of cancer diagnosis and its treatment, including rehabilitation and survivorship. Other therapeutic options may now be displaced as a result of the more clinically or cost-effective alternatives now available. Many established QoL assessment tools were developed well before such treatment advances were available. These treatment advances may present new or additional symptom/side-effect profiles associated with treatment or bring other health-related QoL changes not currently captured. An important question to ask is whether a current QoL assessment tool remains fit for purpose to measure what is important to patients who may be receiving different treatments or interventions, or be at different point of their cancer pathway, from the population who contributed to the development of the tool? The answer to that question can be found by carrying out a literature review and patient interviews – to assess and document content validity [41]. A literature review can also uncover whether post-development trials and studies have identified weaknesses in the tool, for example, poor psychometric performance of scales.

An evaluation of the clinical and psychometric performance of a QoL assessment tool is required to make the case for updating or adapting an existing QoL assessment tool in use. This approach can also be used to assess whether there is merit in merging existing QoL assessment tools, for example, the combination of the EORTC Oesophageal and Gastric Cancer QoL modules to form the Oesphago-Gastro QoL module, the EORTC OG-25 [42].

Updating, adapting or combining an existing QoL assessment tool demands the same scrutiny and scientific rigour as developing an entirely new QoL assessment tool. As such, many of the steps in adapting/updating or combining QoL assessment tools are the same as if you were developing a new QoL assessment tool. A crucial first step is to contact the original module developers. There are several examples in the literature documenting the update of well-established QoL instruments such as the EORTC QLQ lung cancer module [43], and further specific guidance is available [16].

4.4.3 Developing Electronic QoL Assessment Tools

The rise in digital technologies has enabled a corresponding drive to develop electronic-based systems for QoL assessment such as web-based platforms, mobile applications and interactive voice response systems [44] with cancer-specific QoL assessment developers also producing guidance on how to apply and use each instrument, based on international good practice [45]. *Chapter 8* provides an in-depth account of electronic applications of QoL assessment in cancer care.

With respect to the development of QoL assessment tools, attention should be paid if the intention is to use electronic applications. This ensures that any migration from the paper-based format produces equivalent performance when used in an electronic format, albeit these still remain static (fixed) instruments, that is, have fixed items for completion. If minor changes are made, with no change to item content, this can be assessed through usability testing and cognitive debriefing interviews on a small patient sample, representative of the target population [41]. Where more substantial changes are required, such as a change to item wording, or the mode of use changes from visual to oral, more formal equivalence testing would be required. When a QoL assessment requires substantial changes to item content and/or response, full psychometric and usability testing is necessary.

Recent advances have enabled the development of more flexible (adaptable) QoL assessments, underpinned by Computer Adaptive Testing (CAT), in which the items presented to patients are dependent on their answers to previous items. An example is the CAT version of the

EORTC QLQ-C30 [46]. These require specific development approaches to be adopted and are considered in Chap. 9.

4.5 What This Chapter Has Not Covered

Whilst many of the basic design considerations are similar, this chapter has not considered the specific development processes involved in developing preference-based QoL measures to be used in economic evaluations nor quality of care tools. Chapter 15 will consider QoL in the context of generating health utilities and use in economic analysis, and specific guidance for the development of quality-of-care tools is emerging [47].

4.6 Conclusion

The development of robust tools is core to the design, conduct and interpretation of QoL assessment. This chapter has set out the basic foundations and key principles required for the development of a QoL assessment tool and the attention needed to a robust research process.

This attention must start with presenting a compelling evidence-based rationale for developing a tool, including careful description of the population of interest and the intended use of the tool. The process of generating QoL issues, to inform the content validity of the tool, requires careful attention to capture the patient perspective, alongside literature reviews and health professional opinions. This should be followed with careful consideration to the construction of its format and structure. Pre-testing is an important step in assessing the applicability of the tool as a PRO measure. Other considerations, such as translation and developing electronic tools, should be considered during the development process. Whilst the focus has been on developing new tools, many of the steps involved are similar if the intention is to adapt, update or combine an existing tool. The development process can then inform the validation of the QoL assessment tool. Throughout the process of development, working in collaboration with others, and crucially strong patient involvement throughout, brings immense value to the success and quality of the final QoL assessment tool.

As a final note, the development of a QoL assessment tool should not be an isolated activity where the research output is ‘another tool’, but a programme of activity which complements and adds to the tremendous amount of work already in this field. The development process must be considered a means to an end in providing a robust measurement approach which captures meaningful information on the QoL concerns which matter most for the cancer patient and population of interest. The QoL assessment tool can then be applied to measuring QoL within the context of clinical research, healthcare policy or practice.

4.7 Questions That Can Be Used for Learning/Testing

1. Reflecting on what you have learnt from reading previous chapters, what makes developing an assessment tool to ‘measure’ QoL challenging?
2. What would be the potential consequences of poor attention to the development of a QoL assessment tool selected for use in a randomised controlled trial of a new health technology compared to current treatment in patients with cancer?
3. What would be the ethical issues of using a poorly designed QoL assessment tool in a phase III randomised trial of a new therapy where QoL is the primary endpoint?
4. What would be some of the practical challenges associated with developing a QoL assessment tool in a rare cancer population?
5. How could patient involvement be incorporated into creating the rationale (case) for developing a new QoL assessment tool?
6. In comparing the use of focus groups or individual interviews, what are the key strengths and limitations of each approach in generating

QoL issues from a representative sample of patients?
7. What are some of the practical 'user' considerations for developing a mobile app device (on a tablet or smart phone) for collecting QoL data in a clinical trial?
8. What would be specific challenges for developing QoL tools to use in different populations affected by cancer such as older people, people with visual impairments or people living with a learning disability?

4.8 A Topic for Discussion That Can Be Used in Teaching

Using a cancer patient population of your choice, put together (as an individual or small group exercise) a 15-min pitch on what you would do to develop a QoL assessment tool. Focus on explaining:

(a) Why is QoL assessment needed for your population?
(b) What is the purpose of your QoL assessment tool, for example, what aspect of QoL do you intend to measure, what is the population, which part of the cancer pathway such a particular treatment does the QoL intend to cover?
(c) What are the aims for your development?
(d) Briefly describe the key stages to your development process?
(e) Outline some of the main challenges to the research and suggest possible solutions?

4.9 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

- Carlton J, Peasgood T, Khan S, Barber R, Bostock J, Keetharuth AD. An emerging framework for fully incorporating public involvement (PI) into patient-reported outcome measures (PROMs). J Patient Rep Outcomes. 2020;4:4. https://doi.org/10.1186/s41687-019-0172-8.
- Johnson C, Aaronson N, Blazeby JM, Bottomley A, Fayers P, et al. on behalf of the EORTC Quality of Life Group. Guidelines for developing questionnaire modules. 4th ed. EORTC Quality of Life Group; 2011. Available at: https://www.eortc.org/app/uploads/sites/2/2018/02/guidelines_for_developing_questionnaire-_final.pdf. Accessed 2 Mar 2021.
- Patrick DL, Burke LB, Gwaltney CJ, Kline Leidy N, Martin ML, et al. Content validity. establishing and reporting the evidence in newly developed patient-reported outcomes (PRO) instruments for medical product evaluation: ISPOR PRO Good Research Practices Task Force Report: Part 1—eliciting concepts for a new PRO instrument. Value Health. 2011;14:967–77. https://doi.org/10.1016/j.jval.2011.06.
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4.10 Research in Context

The Development of the EORTC QLQ-ELD14

Background

Using the development of the EORTC QLQ-ELD14 [*24*], we share our experience of developing a QoL assessment tool of key decisions that informed the development process. The development processes followed the EORTC guidelines for QoL module development [*18*]. However, whilst such guidelines or principles considered in this chapter provide a basis on which to frame the development of QoL assessment tool, it is important that, where necessary, the development process is tailored to meet the specific requirements of the intended population or setting where the final QoL assessment tool will be used.

Determining the Need and Demand for a QoL Assessment Tool

The initial discussions for a specific QoL assessment tool arose from the development of the EORTC QLQ-PAN26 [*33*] where we noticed that many of the issues affecting QoL in this patient population could be down to age-related health issues (e.g. co-morbidity, frailty) rather than attributed to disease-specific QoL concerns. Following on from this, a scoping paper on current conceptual bases and approaches to capturing health outcomes was published which highlighted the need for specific attention to assessing health outcomes in older people with cancer [*48*]. Further preliminary work and discussion with clinical and QoL experts led to presenting a case to the EORTC QoL group to develop a specific tool for older people with cancer.

Defining the Population of Interest, Purpose and Current Evidence Base

This was one of the crucial elements of the development process and is highlighted as part of the systematic review which was part of the stage 1 development [*49*]. This highlighted the disparity in defining older people, particularly in cancer trials and studies and the variable quality of the evidence base to date. On the basis of the two evidence reviews, involvement of a patient representative who was part of the module development process from the outset, and in consultation with experts from the EORTC QoL group and Task Force for the Elderly, the intended population for the assessment tool was people with cancer aged of 70 years and above, with no upper limit set.

Generating the QoL Items of Specific Interest and Relevance to Older People with Cancer

Patient and healthcare professional (HCPs) interviews were carried out as part of the generation of items, reported in the development paper [50]. The incorporation of in-depth patient interviews enabled a rich description of QoL issues of concern from the perspective of the patient which, combined with the findings of the literature review, resulted in an initial list of issues. Further structured interviews were undertaken with patients and HCPs. Whilst the development followed the EORTC QLG guidelines, specific attention to key issues for each particular tool should also be included in the protocol. An important criterion for this assessment tool was to demonstrate sufficient specificity of health-related QoL concerns for older people aged 70 years and above. To evaluate this, an additional matched comparison group of cancer patients aged 50–69 years was included to determine if QoL issues were of 'general concern' or specific to older people with cancer. Patients also completed the relevant EORTC disease-specific QoL mod-

ule alongside the QLQ-C30 to ensure there was no duplication or redundancy.

Using Other Outcome Measures in the Validation Study

As detailed in the original scoping paper [48], there were a range of assessments employed in assessing health outcome in trials and studies of older people cancer. Although the measures did not assess QoL, it was important to demonstrate the clinical utility of the EORTC QoL module for older cancer patients by providing evidence that it sufficiently complemented the suite of outcomes already used. To determine this, we used known group comparison testing to assess whether the QoL module demonstrated the ability to differentiate between groups based on Charlson co-morbidity score and Geriatric Assessment (G8) score based on pre-determined QoL items (mobility, worries about the future, maintaining autonomy and purpose, and burden of illness scales). This enabled assessment of this aspect of convergent validity on established clinical cut-off points used in older cancer patients. Comprehensive assessment of scale structure, using classic test approaches with item response theory methods as a sensitivity analysis, consideration of patient feedback and an explicit decision trail, led to the final structure and the items retained in the resulting EORTC QLQ-14 [24].

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5 The European Organisation for Research and Treatment of Cancer (EORTC) Measurement System

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5.1 A Brief History of the EORTC Perspective on Quality of Life

The European Organisation for Research and Treatment of Cancer (EORTC) is an organization that is committed to translational and clinical cancer research. It focuses on conducting clinical trials that, over the years, have contributed to progressing the management and treatment of cancer. More specifically, the EORTC's goals are 'to coordinate and conduct international translational and clinical research to improve the standard of cancer treatment for patients. … [ultimately aiming] to increase people's survival and quality of life by testing new therapeutic strategies based on existing drugs, surgery and radiotherapy' [1].

In response to the growing need for structured and coherent quality of life (QOL) research, the EORTC founded the Quality of Life Group (QLG) in 1980. Initially, the group's aim was to support EORTC research in the design and analysis of clinical trials and studies. One of the group's first tasks was to find consensus on how QOL should be defined and measured. The QLG defined health-related quality of life (HRQOL) in a broad sense, taking a perspective set on measuring a wide range of health-related issues that are most likely to be affected by cancer and/or its treatment [2]. This definition of HRQOL not only emphasized the signs and symptoms of the disease but also acknowledged facets of personal functioning such as physical, social, or role functioning. Consequently, HRQOL had to be regarded as a multi-dimensional construct. Finally, the QLG stressed that HRQOL should, whenever possible, be measured by asking the patients themselves. To this day, the patient experience has remained a prerequisite for the development of EORTC HRQOL questionnaires and modules (more information on questionnaire development is given below).

A major milestone was reached in 1987, when the QLG developed the first generation of the EORTC Core Quality of Life Questionnaire (EORTC QLQ-C36, [3]) and the first questionnaire module (the lung cancer module, [4]). Other, more recent, achievements detailed below include the release of the EORTC Computerized Adaptive Testing Core questionnaire (EORTC CAT Core), the EORTC Item Library, and the Quality of Life Utility Measure-Core 10 Dimensions (QLU-C10D).

In the years since its foundation in 1980, the QLG has grown and extended the focus of its work. Its mission, however, has remained largely unchanged: the QLG aims to (1) develop and refine questionnaires to assess HRQOL of patients with cancer, (2) collaborate with EORTC Disease-Oriented Groups in implementing HRQOL studies, and (3) conduct research to better understand the effects of cancer and its treatment on the HRQOL of diverse populations of patients with cancer across different cultures [5]. The following sections provide an overview of the EORTC approach to measuring QOL in patients with cancer and the patient-reported outcome (PRO) measures that have been developed to do so. An overview over the currently available PRO measures developed by the EORTC QLG is given in Table 5.1.

Table 5.1 Overview of available European Organisation for Research and Treatment of Cancer (EORTC) patient-reported outcome (PRO) measures

Measure	Summary information
EORTC Quality of Life Questionnaire Core 30 (EORTC QLQ-C30)	The EORTC QLQ-C30 is the most widely used cancer-specific health-related quality of life questionnaire. Using 30 items organized into 15 scales, it assesses symptoms, functional health, and global health/quality of life. It can be used for the assessment of key PRO domains in patients with all types of cancer.
EORTC questionnaire modules	EORTC questionnaire modules can be used in conjunction with the EORTC QLQ-C30 to assess health issues that are specific for a certain tumour site, treatment modality, or patient population.
EORTC standalone questionnaires	Standalone questionnaires have been developed to assess the patient's perspective on important topics such as satisfaction with care or communication between patients and healthcare professionals. Unlike the questionnaire modules, these questionnaires can be used independently of the EORTC QLQ-C30.
EORTC Computerized Adaptive Testing Core (EORTC CAT Core)	The EORTC CAT Core comprises item banks for all functional health and symptom domains of the EORTC QLQ-C30. These item banks can be used for computerized adaptive testing (CAT) assessments and for creating static short-forms. While static short-forms are sets of questions tailored to a specific patient population, CAT allows the tailoring of assessments even to the individual patient.
	Both CAT questionnaires and static short-forms offer an increase in measurement precision and measurement range compared to standard questionnaires.
EORTC Item Library	The EORTC Item Library comprises a large collection of items to assess diverse aspects of HRQOL (currently 952 individual items). A key purpose of this item bank is to provide additional items for assessing issues not covered by the EORTC QLQ-C30 or its modules. Items from the library can be used to cover toxicities of novel treatments or disease symptoms relevant for specific patient groups.
EORTC Quality of Life Utility-Core 10 Dimensions (QLU-C10D)	The QLU-C10D is a preference-based multi-attribute utility instrument for health economic analyses. It determines patients' preferences for and rankings of different HRQOL domains. Based on the EORTC QLQ-C30, it captures symptoms and functional health utilities that are specific to patients with cancer.

5.2 EORTC Approach to Developing PRO Measures

During the development of the first EORTC questionnaires, an important consideration concerned the appropriate level of measurement specificity, i.e., how specific or generic the questionnaires should be once constructed. A more generic measure allows the comparison of results across different (study) populations, which can be important for influencing larger health policy and cancer research as a whole [2]. However, measures that are more specific can better capture the perspective of specific populations and typically have better measurement capacity in their respective population (meaning they can better detect small but meaningful group differences or changes). Ultimately, a modular approach was chosen to combine the benefits of both generic (the EORTC QLQ-C30, which may be used in all patients with cancer) and specific measures (the disease-specific questionnaire modules).

The QLG has devised a four-stage development process for the development of new questionnaire modules [6]. This highly standardized process ensures the validity and reliability of published EORTC questionnaires and ensures they are kept to the highest standards. A particularly important feature of the development process is the constant inclusion of the patient perspective, especially in the early phases, to ensure content validity and saturation. In detail, the four phases are as follows:

5.2.1 Phase I: Generation of QOL Issues

This phase aims to compile an exhaustive list of relevant QOL issues for the intended domain. This is done by incorporating three sources: (1) a review of the existing literature, (2) interviews with patients from different clinical groups of the target population, and (3) interviews with healthcare professionals with expertise in the target domain. This process ensures that all relevant issues (e.g., symptoms and treatment side effects) for the target population are included in the new questionnaire. Emerging issues are then assessed again by patients and healthcare professionals regarding their relevance, breadth of coverage, and relative importance.

5.2.2 Phase II: Construction of the Item List

In this phase, the issue list developed in Phase I is converted into an item list that conforms to the EORTC QLQ-C30 item format (4-point Likert scale). The potential items are evaluated and compared to existing items from the EORTC Item Library to determine the optimal wording and avoid duplicates. This process may include consultations with healthcare professionals and/or patients.

5.2.3 Phase III: Pre-testing

This phase is used to refine the questionnaire. The provisional questionnaire is first tested in a multi-national study to determine potential problems like redundant or mis-phrased items or missing issues. To ensure compatibility, the new questionnaire is administered along with the EORTC QLQ-C30. Further, patients are asked to assess the items of the new questionnaire regarding their acceptability and applicability. In this phase, a hypothesized scale structure for the questionnaire is developed, which groups items assessing the same construct.

5.2.4 Phase IV: Field-Testing

The aim of this phase is to conduct large-scale international testing of the new questionnaire's scale structure, acceptability, reliability, validity, and responsiveness to change. Studies in this phase typically include diverse patients from the target population. In this phase, three considerations are essential:

1. The questionnaire's acceptability in the target population is determined via structured debriefing interviews.
2. The questionnaire's hypothesized scale structure and its reliability are tested.
3. The validity of the questionnaire is evaluated. Depending on the type of questionnaire, this can be based on clinical or sociodemographic data or other questionnaires. Moreover, the questionnaire is typically evaluated via known-group comparisons (i.e., how well the questionnaire discriminates between clinical groups that are known to differ) and its responsiveness to change (i.e., comparing scores at different clinically important time points, e.g., before and after chemotherapy).

This rigorous process ensures the quality of all EORTC questionnaires and thereby contributes to their wide distribution and usage. While it is mainly used to develop disease-specific modules, a similar process is used to develop computerized adaptive testing (CAT) measures (which have a stronger developmental focus on IRT [7–9]) and standalone EORTC questionnaires (such as the EORTC PATSAT-C33). Finally, an update to the guidelines is currently being performed and changes may include moving the evaluation of factor structure forward to Phase III to prevent any changes following the final Phase IV.

5.3 EORTC QLQ-C30

The EORTC QLQ-C30 [10] is a cancer-specific HRQOL questionnaire with 30 items organized into 15 scales. There are five multi-item functional scales (physical, role, social, emotional,

and cognitive functioning), three multi-item symptom scales (fatigue, pain, nausea/vomiting), six single-item symptom scales (dyspnoea, insomnia, appetite loss, constipation, diarrhoea, financial difficulties), and a two-item global health/QOL scale. All questions are answered on a 4-point Likert-type scale (response categories: not at all, a little, quite a bit, very much), with the exception of the two items of the QOL scale, which use a 7-point scale. For the functioning and the QOL scales, a higher score indicates better functioning. For the symptom scales, a higher score indicates a higher level of symptom burden.

The EORTC QLQ-C30 has been translated into more than 100 languages and, as of March 2021, has been used in more than 4200 studies listed on PubMed. There is a plethora of psychometric validation studies available in the literature investigating a range of aspects of validity in various patient populations (e.g., content validity and evaluation of different modes of administration such as paper-pencil, electronic devices, and interviews [11, 12]). It has been the most frequently used questionnaire in clinical trials [13] and daily clinical practice [14].

For palliative care, a 15-item short-form of the EORTC QLQ-C30 has been developed, the EORTC QLQ-C15-PAL [15]. This short-form assesses key aspects of HRQOL in palliative cancer populations with a short life expectancy and high symptom levels.

Recently, the QLQ-C30 Summary Score has been introduced [16] as an additional scoring method, since in a clinical trial context, the detailed information provided by the HRQOL profile can be problematic with regard to multiple testing and alpha error inflation. Following considerations on model fit and parsimony, a single-factor model (covering all domains with the exception of financial impact and global QOL) was selected as the basis for the QLQ-C30 Summary Score. The QLQ-C30 Summary Score has been shown to be as discriminative as the best performing single scales of the QLQ-C30 with regard to tumour stage, performance status, and change over time [16] and has recently also been replicated and validated in haematological patients [17].

For health economic analyses, health utility values can be calculated from the EORTC QLQ-C30 (please see below for further details).

5.4 Disease-Specific Modules

Following the modular approach to measuring HRQOL in patients with cancer, the EORTC QLG has developed module questionnaires (see paragraph on developing PRO measures, above) that assess issues which are specific for a certain tumour site, treatment modality, or patient population. Importantly, the module questionnaires are to be used in conjunction with the EORTC QLQ-C30, as issues covered by the EORTC QLQ-C30 are not assessed in the module questionnaires.

The first module questionnaire was the lung cancer module (EORTC QLQ-LC12), which was developed together with the first version of the Quality of Life Core questionnaire, the EORTC QLQ-C33. Some examples of module questionnaires include the EORTC QLQ-BR45 for patients with breast cancer, the EORTC QLQ-CIPN20 for patients with chemotherapy-induced neuropathy, and the EORTC QLQ-FA12 for patients with cancer-related fatigue.

As of March 2021, there were a total of 51 module questionnaires covering the most prominent tumour sites and patient populations. Generally, the EORTC QLG considers module questionnaires fit for usage in clinical trials after successful completion of Phase III of the development process. However, the final factor structure may change in Phase IV validation. Currently, there are 27 modules with Phase IV validation, 17 modules with Phase III validation, and 7 modules that are under development in Phases I and II (see https://qol.eortc.org/modules/ for an overview).

5.5 Standalone Questionnaires

Standalone questionnaires cover important aspects of QOL that are not specific to a single tumour site. They address issues or QOL domains that are not covered by the EORTC QLQ-C30 but are relevant for patients with cancer (e.g., patient satisfaction with care). Unlike the module questionnaires, standalone questionnaires do not need to be used in conjunction with the EORTC QLQ-C30 and can be used on their own.

The EORTC QLG has developed several standalone questionnaires that address different aspects of patients' QOL (https://qol.eortc.org/standalone/). These include:

- The EORTC QLQ-COMU26, which assesses the quality of communication between patients and healthcare professionals
- The EORTC QLQ-PATSAT-C33, QLQ-INPATSAT32, and QLQ-OUT-PATSAT7, all of which assess patient satisfaction with cancer care (in general, for inpatients and for outpatients, respectively)
- The EORTC QLQ-SHQ-22, which covers aspects of patients' sexual health
- The EORTC QLQ-SWB32, which covers aspects of patients' spiritual well-being.

The EORTC QLG has also identified the need to develop standalone questionnaires for cancer survivors, which aim to capture their specific physical, mental, and social HRQOL issues after the completion of treatment [18].

5.6 EORTC CAT Core and Static Short-Forms

Static short-forms and computerized adaptive testing (CAT) allow for more flexible measurement of PROs than traditional PRO measures, such as the EORTC QLQ-C30 (see also Chap. 9, this volume). While traditional measures use the same set of questions for all patients, comprehensive item banks based on item response theory (IRT) measurement models allow assessments with item sets (i.e., static short-forms) that are most appropriate for a specific patient population [19] or assessments that are even tailored to the individual patient, using an algorithm that in a stepwise procedure selects the most informative item to be asked next based on the patient's previous responses (e.g., if a patient reports not being able to go for a short walk, further questions will focus on basic tasks such as dressing or eating, and not cover physically challenging activities). Both CAT and static short-forms can be created to meet predefined criteria for measurement precision or assessment length and can additionally balance item content if specific aspects of domain need to be covered. Thanks to the underlying IRT measurement model, scores derived from static short-forms and CAT assessments relying on the same item bank are directly comparable, which is an important advantage over traditional PRO measures which build on classical test theory and require the administering of the same items to all patients. Unlike CAT assessments that necessarily require an electronic mode of administration (e.g., mobile phones or tablets), the static short-forms can also be administered on paper.

The EORTC CAT Core [8, 9] has been developed within a series of projects including about 10,000 patients from 12 countries by the EORTC Quality of Life Group since 2005. The aim of these projects was to develop item banks for the computerized adaptive testing (CAT) and for the creation of static short-forms for each of the functional health and symptom domains covered by the EORTC QLQ-C30. The item bank consists of a total of 260 items with 7–34 items per domain and is currently available in a number of (mostly European) languages. All functional health and symptom domains of the EORTC QLQ-C30 are included in this item bank, and scores from the EORTC CAT Core are fully backward compatible with the EORTC QLQ-C30 scores.

All item banks have been developed in a multistep process comprising an extensive literature search to identify potentially relevant issues for each domain, the creation of items based on these issues that are in line with the general EORTC item style, patient and expert interviews to evaluate the items, and finally field-testing and com-

prehensive psychometric analyses to evaluate the measurement characteristics of the individual items and the validity of the item bank.

The increased measurement precision of the EORTC CAT Core allows the detection of clinically relevant differences with a higher accuracy and thus helps to reduce sample size in clinical studies. In comparison to the EORTC QLQ-C30, the EORTC CAT Core provides the same statistical power with a 20–35% smaller sample size [8, 20]. Sample size savings may be an important feature of these new measures in the context of clinical studies as it may help to reduce study duration and costs. At the level of the individual patient, the higher measurement precision results in smaller detectable changes and thus better identification of improvements or deteriorations in clinical practice. Finally, in a previous study [21], results indicated that patients may perceive the individually tailored CAT items as more appropriate for their current condition than those from traditional questionnaires. Further information on the EORTC CAT Core can be found on its official website (https://qol.eortc.org/cat/).

5.7 EORTC QLU-C10D

The EORTC QLQ-C30 has long been used in clinical research and more recently also in daily clinical practice, where the individual functional health and symptom domains provide a detailed picture of a patient's health. For health economic research, however, this multi-domain structure of the EORTC QLQ-C30 is limited in its applicability, as the general interest and focus of health economic analyses is an overall assessment of a patient's health that can be related, for example, to treatment costs and/or survival time.

To make the EORTC QLQ-C30 more applicable for such a purpose, a preference-based scoring algorithm allowing the calculation of cancer-specific utilities has been developed: the Quality of Life Utility-Core 10 Dimensions (QLU-C10D).

The Multi-attribute Utility in Cancer (MAUCa) consortium [22], an international group of HRQOL researchers, developed the QLU-C10D by selecting the most relevant domains through a mixed-methods approach including IRT analyses and patient and expert interviews. The work has resulted in a health description system consisting of 13 items of the EORTC QLQ-C30 that cover 10 domains: physical functioning, role functioning, social functioning, emotional functioning, pain, fatigue, insomnia, appetite loss, nausea, and bowel problems. Accordingly, the health state of an individual patient can be described with a 10-digit number assigning one digit to each domain based on the response categories of the items (1 = "not at all" to 4 = "very much"). Please note that the QLU-C10D domains are not identical to the EORTC QLQ-C30 domains, as they may only comprise part of the items (e.g., physical functioning or nausea) or may combine domains (e.g., bowel problems).

Using discrete-choice experiments that relate individual health states to survival time [23, 24], a scoring algorithm was developed to calculate the utility value of each health state which represents a continuum from 0 (a health state equalling death) to 1 (full health). Values below 0 are considered to represent health states rated as worse than being dead. Health utility values are used mostly for cost-utility analysis in pharmacoeconomic research, for weighting survival time by health state to obtain quality-adjusted life years (QALYs).

With the availability of the QLU-C10D, important data for cost-utility analyses can be collected in studies using the EORTC QLQ-C30 without the need to lengthen the assessment through the use of additional questionnaires, but more importantly, the wealth of previously collected EORTC QLQ-C30 data can now be analysed for health economic purposes.

Since patient preferences for specific health states may differ across cultures, the utility weights for each health state are determined separately for individual countries. Currently, country-specific weights for the EORTC QLU-C10D are available for a number of countries, including Australia, Austria, Canada, France,

Italy, The Netherlands, Poland, and the UK, and further projects are ongoing, for example, in China, Japan, and Spain.

A manual to guide the application of the EORTC QLQ-C10D, including a scoring syntax for common statistical software packages, is currently being drafted and will be available on the EORTC Quality of Life Group website (https://qol.eortc.org/manuals/).

5.8 EORTC Item Library

In a current debate within the FDA and other regulatory authorities [25–27], the content validity of available HRQOL questionnaires has been questioned, as the rapid progress in the development of new cancer drugs may result in insufficient coverage of treatment toxicity by traditional PRO measures. The most frequently used PRO measurement systems in cancer have mostly relied on core questionnaires supplemented with questionnaire modules that comprise fixed sets of domains for patient groups defined by diagnosis but are not specific for individual substances or combinations thereof. The flexibility to swiftly react to the assessment needs in clinical trials assessing HRQOL and toxicity related to new drugs therefore may not be sufficiently provided by current PRO measures that are based on development processes usually lasting several years from content generation to psychometric validation.

The EORTC has responded to this debate through the release of the EORTC Item Library (https://www.eortc.be/itemlibrary/), which allows the extension of current HRQOL questionnaires with additional items that cover drug/treatment-specific issues and toxicities to enable a comprehensive and valid assessment of new drugs. The EORTC Item Library currently comprises 952 unique items in up to 110 languages. These items originate from 67 previously developed EORTC measures. Upon request to the EORTC Quality of Life Group, users can obtain access to this online database that provides multiple search options and a questionnaire builder. A key purpose of this item bank is to provide additional items for assessing issues not covered by the EORTC QLQ-C30 or its modules. While the abovementioned item banks of the EORTC CAT Core allow an increase in measurement precision and measurement range of the PRO domains included in the EORTC QLQ-C30, the EORTC Item Library allows the addition of extra content to cover novel toxicities or disease symptoms relevant for specific patient groups.

A good example of how to use the EORTC Item Library has been published by Bell et al. [28], in which the authors describe the selection of items for the assessment of clinical benefit in clinical trials in patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia, and acute myeloid leukaemia. Their multi-step process aims at selecting relevant items that may need to be added to the core questionnaire EORTC QLQ-C30 and its questionnaire modules. The process builds on a literature review, clinician consultation, and patient interviews and includes qualitative and quantitative analyses.

In a study by Mouillet et al. [29] evaluating the benefits of symptom monitoring in daily clinical practice of patients with renal cell carcinoma treated with a tyrosine kinase inhibitor, the EORTC QLQ-C30 was supplemented with six domains (epigastralgia, mouth pain, skin toxicity, hair loss, taste changes, and bone pain) to capture frequent adverse events related to sunitinib and pazopanib.

At the moment, a technical guide covering practical aspects of the use of the EORTC Item Library is already available, while a scientific guide detailing a measurement strategy making optimal use of the database is being drafted and will be available on the EORTC Quality of Life Group website (https://qol.eortc.org/manuals/).

5.9 Scoring and Interpretation of EORTC Measures

Scoring algorithms combine patients' responses to one or more questions assessing the same health domain into a single variable or value. This can be used to summarize responses given by patients and allows for easier interpretation

(e.g., by obtaining a score for 'fatigue' by summarizing patients' responses to the three items of the EORTC QLQ-C30 that measure aspects of fatigue). The EORTC QLG has published scoring algorithms for the EORTC measures, which also include scoring syntaxes for the most common statistical programs [30]. Currently, the guidelines are being revised and an updated version will be published soon.

While the interpretation of single answers may be warranted in individual consultations or for specific questions, the EORTC QLG generally recommends the usage of scales that have been validated during the questionnaire's development. Items that belong to a scale are mostly summed and linearly transformed to obtain a scale score on a metric ranging from 0 to 100. Importantly, the minimum and maximum of the metric do not represent the lowest and highest possible symptom level, but represent only the limit of the measurement range. When interpreting scores, it is crucial to consider the scale direction: while for functioning scales high scores indicate good health, for symptom scales high scores reflect high symptom burden.

The scoring of the EORTC CAT Core cannot be obtained via linearly transformed sum scores. Instead, the EORTC CAT Core is scored using standardized T-scores that rely on a normative metric obtained from a reference population (general population [31]). T-scores are standardized to a fixed mean of 50 points (the mean of the reference population) and a standard deviation of 10 points. This means that T-scores not only are a scoring method but also already contain a means of interpretation (as single scores are compared to the reference population).

5.9.1 Interpretation Approaches for EORTC Measures

The EORTC QLG has established different approaches to support the meaningful interpretation of scores from EORTC measures. These include normative data, thresholds for clinical importance (TCIs), and minimal important differences (MIDs).

5.9.1.1 Normative Data

The PRO scores from individuals or groups can be compared to normative data from a reference population of interest. This reference population can either be the general population or a comparable patient population (e.g., a sample with similar diagnosis, disease status, or treatment). Comparisons to the general population may be useful for the analysis of cancer survivorship data, i.e., if patient HRQOL is expected to mostly return to general population levels. Comparisons with patient populations may be more meaningful for patients undergoing treatment or in advanced stages of the disease. In a large-scale project, the EORTC QLG has established international general population normative data for both the EORTC QLQ-C30 [32] and the EORTC CAT Core [31]. Moreover, normative data from the general population for many individual countries can be found in the literature [33–36]. For the comparison of PRO scores with patient populations, normative data from patients with cancer can be used [37, 38] and alternatively data from cancer registries are increasingly being made available. For example, the Dutch Patient Reported Outcomes Following Initial treatment and Long-term Evaluation of Survivorship (PROFILES) registry [39] holds large amounts of data from Dutch patients with cancer that are freely available for academic usage. Finally, the EORTC QLG has set up a data repository with data from clinical trials and projects that can be requested by researchers [40].

5.9.1.2 Thresholds for Clinical Importance

Another method of interpreting PRO data is Thresholds for Clinical Importance (TCIs), which have been developed for the EORTC QLQ-C30 [41], the EORTC QLQ-PAL15 [42], and the EORTC CAT Core [43]. The TCIs have been anchored to patients' responses to indicate clinically important problems in at least one of three anchor criteria: (1) limitations of daily functioning, (2) need for help or treatment, and (3) worries by the patient or his/her partner or family. These anchor criteria have been established based on qualitative and quantitative data

from cancer patients and healthcare professionals [44]. Patients scoring above the established thresholds for functioning scales or below the thresholds for symptom are considered to have severity levels requiring further clarification by a healthcare professional.

The threshold values are particularly useful for the interpretation of PRO data in clinical practice, as they are easily understandable and can be used to quickly highlight important impairments. However, they can also be used to analyse group-level data, e.g., by calculating the percentage of a population that scores above or below the TCI. This may be used to elicit prevalence rates for clinically important impairments, which can be compared to other data sources (e.g., clinician ratings). A project is currently being conducted to determine TCIs for questionnaire modules.

5.9.1.3 Minimal Important Differences

As implied by its name, a minimal important difference (MID) provides information if a change over time (experienced by an individual or a patient group) or a difference between two groups is actually clinically meaningful. Different to the term of statistical significance, which indicates the probability of chance findings, MIDs provide information on whether the differences between groups or measurement time points carry clinical weight. For example, a finding may be statistically significant (e.g., a two-point decrease in patient-reported pain on a scale of 0 to 100) but not clinically important. Therefore, MIDs can be an especially important interpretation approach for large-size clinical trials with high statistical power that are hence able to find small yet statistically significant differences in PROs.

There is a diverse, not completely harmonized terminology around MIDs that refers to similar or the same concepts, known as, for example, *minimal clinically important difference* or *clinically relevant difference* (for a critique and classification, see [45]). Moreover, there are different approaches to defining MIDs: firstly, they can be established on either an individual or a group level. Secondly, they may follow an anchor-based (e.g., transition items assessing perceived change over time [46]) or a distribution-based (e.g., effect size [47]) approach. These distinctions determine for what kind of analyses the respective MIDs can be used.

Early MID values for EORTC measures were published by Osoba et al. [48], who determined limits for small (5–10 points), moderate (10–20 points), and large (>20 points) changes in EORTC QLQ-C30 scores. However, as pointed out by King [49], the score range for small, medium, or large effects often differs between HRQOL scales. Studies by Cocks et al. [50, 51] showed that thresholds for differences vary not only between HRQOL scales but also between the direction of change (improvement or deterioration) and in different settings. Consequently, there is no 'one size fits all' approach to MIDs, and different MIDs are warranted for different kinds of interpretation and samples [45, 47, 52].

In several projects, the EORTC has developed MIDs for patients with malignant melanoma [53], glioma [54], ovarian cancer [55], advanced breast cancer [56], head and neck cancer [57], and colorectal cancer [58].

5.9.2 Visualization of PRO Data

Especially for users who are inexperienced in the usage and interpretation of PRO data, the visual presentation of the results is crucial for making sense of the data. There are different approaches to visualizing PRO data, which can vary depending on the goals of the visualization (displaying individual- or group-level data) and the familiarity of users with PRO data. Whenever possible, PRO data should be made available not only for healthcare professionals but also for patients themselves. In a study by Oerlemans et al. [59] using EORTC measures, 80% of patients reported the wish to receive PRO feedback. Importantly, the optimal graphical presentation for patients and healthcare professionals can differ [60]. Moreover, the display of PRO results should be accompanied by sufficient interpretation guidance, as highlighted in a study by Kuijpers et al. [61].

The Patient-Centered Outcomes Research Institute has published guidance on the graphical display of PRO data to optimize their accurate

and meaningful interpretation [62]. This involved a consensus panel which, among others, included cancer survivors and caregivers. The recommendations provide in-depth guidance on issues such as scale directionality (which is different for EORTC functioning and symptom scales), score meaning (e.g., what is a 'severe' result?), the optimal visualization for individual patient data, and how to display or highlight important scores (see also Chap. 12, this volume).

5.10 EORTC Measures in Clinical Research and Practice

The EORTC measures have historically been used for assessing outcomes in clinical trials and observational studies to evaluate the impact of cancer and its treatment from the patient perspective. In clinical trials, the measures have mostly been used as secondary or exploratory endpoints to provide information on HRQOL and/or treatment toxicity [63], e.g., to demonstrate non-inferior HRQOL for experimental treatments that provide clinical benefits in terms of survival. More rarely, primary trial endpoints have been assessed with the EORTC measures, in particular in palliative care settings [64], to show superiority of new treatments regarding pain, fatigue, or HRQOL. In a recent analysis [63] of 229 cancer trials using the EORTC QLQ-C30, about 60% of trials found a difference between the experimental and the control groups. The scales most frequently showing such differences were global QOL, physical functioning, fatigue, nausea/vomiting, and role functioning. The finding from this analysis, that differences between treatment arms are typically reported for combinations of functional health, symptoms, and global QOL, underlines the importance of multidimensional PRO assessments to adequately cover the overall treatment burden. In observational studies, the EORTC measures have been shown, for example, to be important prognostic factors of patient survival that increase prognostic accuracy beyond known clinical characteristics [63, 65]. In a recent meta-analysis [65], the EORTC QLQ-C30 was found to be the most frequently used measure in such studies. Among its scales, the physical functioning scale was the most important independent prognostic factor for overall survival.

With the publication of the EORTC QLU-C10D, the EORTC now also provides a health utility measure that enables the use of EORTC QLQ-C30 data for health economic cost-effectiveness or cost-utility analyses. While this has been introduced only recently, it may be a valuable contribution to this type of analysis as it enables the use of large amounts of previously collected data. Another more recent application of the EORTC measures is their integration into cancer registries [39, 66], to routinely collect comprehensive real-world data on HRQOL and treatment toxicities, from patient populations that may often be under-represented in clinical trials.

In addition to their use for clinical research, the EORTC measures have also proven valuable in routine clinical practice over the years. The multidimensional structure of the EORTC QLQ-C30 and its questionnaire modules make these measures particularly useful for clinical practice, as they provide detailed profiles rather than aggregate outcomes scores that may be useful in a clinical trial context but are less actionable in clinical practice. As summarized by Wintner et al. [60], there is concrete evidence that EORTC measures can support the communication between patients and clinicians [67, 68], increase clinicians' awareness of patients' health status [69, 70], and support shared decision-making in oncology [71]. Nonetheless, the implementation of routine PRO monitoring is challenging with a number of barriers that need to be overcome [72].

To support the use of the EORTC measures in clinical practice, the EORTC QLG has released a manual for the usage of EORTC measures in daily clinical practice [60, 73] to support the successful implementation of PRO monitoring. This manual covers a number of key aspects of the planning and implementation of routine PRO monitoring. Planning of routine assessments with the EORTC measures includes, for example, the selection of appropriate measures and time points to monitor HRQOL in a specific patient population. Regarding selection of measures, it is generally recommended to use the EORTC QLQ-C30

as a core measure and extend it with disease-specific modules and/or additional items from the EORTC Item Library. Regarding the frequency of assessments, there is only limited evidence-based guidance and variation across settings that is necessarily considerable, e.g., due to heterogeneity of treatment regimens and disease trajectories. Therefore, expert opinion and patient feedback should be used to ascertain the optimal frequency to guarantee adequate coverage of clinically relevant time points. In cases where PROs are assessed repeatedly, the frequency of assessments should balance a sufficient depth of information and granularity of PRO data with an acceptable burden of assessment for patients; i.e., a short assessment may be distributed at shorter intervals, while longer assessments may be given at prolonged intervals. The most feasible mode of administration, also recommended by the EORTC QLG [60], is electronic questionnaire administration on, e.g., tablet PCs or mobile phones. Electronic means of data collection are almost inevitable when using PRO data for daily clinical practice, as they allow immediate access to collected PRO data by healthcare professionals and can support the interpretation of PROs by integrating normative values, thresholds, or MIDs in the graphical presentation of results from individual patients.

Next to specific aspects of PRO monitoring such as selection of PRO measures and assessment time points, the EORTC manual on the use of the EORTC measures in clinical practice [73] also provides a number of more general, practical considerations and issues that should be taken into account during the process of implementing routine PRO monitoring. The following list gives an overview of key considerations detailed in the manual for successful implementation:

1. Develop an understanding of current practice: Before developing implementation strategies, make sure you understand current practice and acknowledge it in your approach.
2. Involve all relevant stakeholders: The implementation process should involve all healthcare professionals; if possible, assign an implementation coordinator.
3. Ensure that healthcare professionals regard PRO measures as relevant: Involve healthcare professionals in the selection of PRO measures to facilitate the uptake of EORTC measures.
4. Make data actionable: PRO data needs to be made 'actionable', e.g., by flagging results that exceed the TCIs [41].
5. Offer training and support: Introduce healthcare professionals, as well as patients, to PROs and offer support.
6. Evaluate the processes and outcomes: Clearly define outcomes for successful implementation and reflect on the progress.
7. Consider the organizational context: Organizational changes will most likely be necessary; consider necessary action and plan accordingly.
8. Evaluate long-term success: Evaluate if PROs have been successfully and sustainably implemented (e.g., via an observational or quasi-experimental study).

Naturally, this is not an exhaustive list, and unforeseen, more specific, issues may arise. The implementation of PRO monitoring is a complex intervention which takes place in unique healthcare settings. Consequently, the facilitators and drivers for change can be context specific and a customized approach should be developed. Nonetheless, manuals can provide very valuable support for the implementation process, as despite huge variability of settings and conditions in PRO implementation, barriers to the implementation process can be surprisingly similar [74].

5.11 Conclusion

The various standalone questionnaires, the questionnaire modules, and the EORTC Item Library provide flexibility regarding the coverage of broad HRQOL domains and specific symptoms and toxicities, while the EORTC CAT Core allows flexible adaptation of measurement precision and assessment lengths to

specific needs. To support the application of the EORTC measures and provide background information as well as context, the EORTC QLG provides a number of manuals (https://qol.eortc.org/manuals/). Several of these manuals are currently being updated to reflect new developments within the EORTC QLG and the general field of PRO research. Further, new manuals, for example, on how to interpret the EORTC measures and on how to use the EORTC Item Library are expected in the near future. In conclusion, data collected with the EORTC measures can provide crucial information from the patients' perspective on the clinical benefits, safety, and tolerability of cancer treatments, making these measures important for both clinical research and clinical practice.

5.12 Questions That Can Be Used for Learning/Testing

- Please summarize the four development phases for PRO measures formulated by the EORTC QLG. Which phase needs to be completed before: (a) the questionnaire is tested in a multinational study; (b) an item list can be constructed; and (c) the questionnaire can be used in a full-scale study/trial?
- What are the advantages of the EORTC CAT Core over traditional PRO measures?
- How can scores from PRO measures be interpreted with the help of thresholds for clinical importance?
- What are three key issues that need to be considered when implementing PRO monitoring into daily clinical practice?

5.13 A Topic for Discussion That Can Be Used in Teaching

In a clinical trial context, the definition of appropriate PRO endpoints can be a challenging task. Please discuss strategies for determining the PRO domains that are most suitable for being a primary or secondary trial endpoint in a specific trial and debate considerations on how to select the optimal PRO measure for assessing this endpoint.

5.14 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

- *Example of an EORTC questionnaire module update:*
- Koller M, Shamieh O, Hjermstad MJ, Hornslien K, Young T, Chalk T, et al. Psychometric properties of the updated EORTC module for assessing quality of life in patients with lung cancer (QLQ-LC29): an international, observational field study. Lancet Oncol. 2020;21(5):723–32.
- *Example of the use of the EORTC Item Library:*
- Bell JA, Galaznik A, Pompilus F, Strzok S, Bejar R, Scipione F, et al. A pragmatic patient-reported outcome strategy for rare disease clinical trials: application of the EORTC item library to myelodysplastic syndromes, chronic myelomonocytic leukemia, and acute myeloid leukemia. J Patient Rep Outcomes. 2019;3(1):35.
- *Interpretation of EORTC measures:*
- Giesinger JM, Aaronson NK, Arraras JI, Efficace F, Groenvold M, Kieffer JM, et al. A cross-cultural convergent parallel mixed methods study of what makes a cancer-related symptom or functional health problem clinically important. Psychooncology. 2018;27(2):548–55.
- Cocks K, King MT, Velikova G, Martyn St-James M, Fayers PM, Brown JM. Evidence-based guidelines for determination of sample size and interpretation of the European Organisation for the Research and Treatment of Cancer Quality of Life Questionnaire Core 30. J Clin Oncol. 2011;29(1):89–96.

- *Use of the EORTC QLQ-C30 for survival prognosis:*
- Efficace F, Collins GS, Cottone F, Giesinger JM, Sommer K, Anota A, et al. Patient-reported outcomes as independent prognostic factors for survival in oncology: systematic review and meta-analysis. Value Health. 2021;24(2):250–67.
- *Example of a Phase III clinical trial using EORTC measures:*
- Roussel M, Moreau P, Hebraud B, Laribi K, Jaccard A, Dib M, et al. Bortezomib, thalidomide, and dexamethasone with or without daratumumab for transplantation-eligible patients with newly diagnosed multiple myeloma (CASSIOPEIA): health-related quality of life outcomes of a randomised, open-label, phase 3 trial. Lancet Haematol. 2020;7(12):e874–83.
- *Guidelines for the inclusion of PRO measures in clinical trials:*
- Calvert M, Kyte D, Mercieca-Bebber R, Slade A, Chan AW, King MT, et al. Guidelines for inclusion of patient-reported outcomes in clinical trial protocols: the SPIRIT-PRO extension. JAMA. 2018;319(5):483–94.
- *Use of PRO measures in clinical practice:*
- Wintner LM, Sztankay M, Aaronson N, Bottomley A, Giesinger JM, Groenvold M, et al. The use of EORTC measures in daily clinical practice-a synopsis of a newly developed manual. Eur J Cancer. 2016;68:73–81.
- Mouillet G, Falcoz A, Fritzsch J, Almotlak H, Jacoulet P, Pivot X, et al. Feasibility of health-related quality of life (HRQoL) assessment for cancer patients using electronic patient-reported outcome (ePRO) in daily clinical practice. Qual Life Res. 2021.
- Aaronson NK, Elliott T, Greenhalgh J, Halyard MY, Hess R, Miller D, et al. User's guide to implementing patient-reported outcomes assessment in clinical practice. 2015. [Internet, cited 2021 Mar 17]. Available from: https://www.isoqol.org/resource-center/.

5.15 Research in Context

The systematic review by Koller et al. [75] provides an overview of the use of the EORTC lung cancer module (QLQ-LC13) in clinical trials covering a 20-year period. Within this period, the QLQ-LC13 was used in 109 randomized controlled trials, most of which were Phase III trials. The QLQ-LC13 was used as a primary endpoint in 20 of those trials (18.3%). Differences between treatment arms were detected in 47 trials for the QLQ-C30 and in 36 trials for the QLQ-LC13. In about one-third of the trials, differences in PROs were discordant with the survival endpoint (differences between treatment arms in PROs but not in survival and vice versa), highlighting the additional value of PRO endpoints in clinical trials. Since the original release of the QLQ-LC13, treatment of lung cancer has advanced substantially. To more adequately cover the toxicity of new treatments, the lung cancer module has recently been updated, resulting in the release of a new version, the QLQ-LC29 [76].

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6 The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System: Guidance for Use in Research and Clinical Practice

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6.1 Introduction

Over the course of the last half-century, patient-centered outcomes have risen to a prominent position in health research and clinical practice. Historically, in oncology, survival has been considered (and to a large part still remains) the definitive treatment goal. However, advancements in the conceptualization of patient-prioritized endpoint frameworks, increased methodological rigor in measurement science, and the proliferation of meaningful health outcomes data have galvanized medical, research, and regulatory communities to increase the value placed on quality of life and quality of survival. Health-related quality of life (HRQoL) has emerged as the defining construct which encompasses multiple primary domains of physical, functional, social, and emotional well-being, and represents concerns that, by definition, are best assessed by asking patients directly. HRQoL assessment quantifies disease- and treatment-related symptom presence, frequency, and/or intensity and the impact of health status on components of health and functioning [1–3]. Given advancements in, and expanding options for the clinical and therapeutic management of cancer, HRQoL and other patient-reported outcomes (PROs) have emerged as highly relevant endpoints in clinical research and practice.

In 2009, the Food and Drug Administration (FDA) released guidance for industry regarding the use of PRO measures to support labeling claims, indicating that this new era of outcomes assessment had reached a point of serious regulatory attention. Patient-reported outcomes are defined as "any report of the status of a patient's (or person's) health condition, health behavior, or experience with healthcare that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [4]" and are especially germane in oncology research and practice. In 2020, it is estimated there were 1,806,590 new cases and 606,520 deaths from cancer, making it the second leading cause of death in the United States [5]. Advances in screening and more successful treatment options have led to almost 17 million US cancer survivors in 2019 [6], with cancer now regarded as a chronic condition [7]. Survivorship, however, can be associated with debilitating disease and treatment-related symptoms along with functional and emotional sequelae. In addition, a vast array of existing and emerging treatment modalities and protocols (ranging from those that are highly aggressive with curative intent to palliative regimens) and their attending toxicity profiles create a complex landscape for decision-making where benefit has to be weighed along-side toxicity. In aggregate, factors associated with incidence, survivorship, chronicity, incurability, and treatment-related adverse events complicate the short- and long-term management of cancer and pose significant challenge to clinicians in terms of treatment decision-making, supportive care, and symptom relief. PROs can help navigate these waters.

Ensuring that the patient-perspective is represented in treatment decision-making becomes paramount to achieve quality, patient-centered care [8]. In cancer, PROs bring the patient-perspective to the fore and can contribute significantly to our understanding of patients' experiences with symptoms, treatment, and their impact on HRQoL. In clinical trial evaluations, PROs can enhance our understanding of "efficacy" and value in face of treatment toxicity and HRQoL [9–12], including more accurate assessment of adverse event burden and how such toxicities influence the therapeutic risk-benefit ratio. In clinical practice, PROs support early symptom detection, symptom monitoring and management, and patient-centered treatment decision-making [13–18]. Emerging applications in health system management [19] and regulatory approvals [20] have also increased considerably [8, 21].

Advancements in PRO assessment, including measurement science and technologies for data capture and delivery and a robust and growing body of literature demonstrating value, have permitted widespread acceptance, use, and adoption of PRO assessment in clinical trial evaluations and at the point of care. Greater methodological rigor in measure development has produced a host of valid and reliable PRO measures and measurement systems for global and targeted HRQoL assessment across diseases, conditions, and therapeutic interventions. Innovative techniques in data analysis and interpretation have greatly enhanced our ability to meaningfully interpret and apply results. While paper and pencil administration has been the standard mode for data collection; innovations in technology over the past 20 years have improved efficiency via electronic data capture, including by telephone using interactive voice response (IVR), computer tablet, and smartphones, and allow for the direct delivery of data to a database or portal, including electronic health records (EHR).

Over the past four decades, as HRQoL assessment has become increasingly prominent across medical research and healthcare, the Functional Assessment of Chronic Illness Therapy (FACIT) has grown similarly. Beginning in 1988 with version 1 of the Functional Assessment of Cancer Therapy (FACT), it has expanded to include multiple cancer site-specific subscales and measures designed for several chronic conditions, disease symptoms, treatment side effects, and other patient-centered outcomes [7]. This chapter describes the FACIT Measurement System and reviews its applications in research and clinical care.

This chapter will enable the reader to better understand: (a) The value of patient-reported outcomes (PROs), including health-related quality of life (HRQoL). (b) The definition, guiding conceptual framework, and domains of HRQoL. (c) Patient-centered methods for PRO measure development, validation, and multilingual translations, with illustrations from the FACIT Measurement System. (d) Considerations when evaluating/selecting a PRO measure, with illustrations from the FACIT Measurement System. (e) Interpretation of PRO scores using reference or normative values, clinical anchor variables, published information on important group differences and important change for groups, and responder definitions at the individual level, as illustrated by the FACIT Measurement System. (f) Considerations for implementation and use of PROs in research and clinical settings.

6.2 History of FACT and FACIT

6.2.1 Conceptual Framework

The Functional Assessment of Chronic Illness Therapy (FACIT) Measurement System, under development since 1988, is a comprehensive collection of patient-reported measures that assess general HRQoL and specific disease- and treatment-related concerns across multiple chronic illnesses and the general population. The measurement system (originally referred to as the Functional Assessment of Cancer Therapy, or FACT) emerged from a conceptual framework for quality of life in the context of health status that is centered on two essential principles: subjectivity and multidimensionality [1, 22, 23]. HRQoL is uniquely personal, defined by patient experiences and influenced by one's subjective

perspective. Therefore, HRQoL is best assessed by direct-report. HRQoL is multidimensional, including, but not limited to symptoms, side effects, and functional status. It also includes more general appraisals of life quality and value. Meaningful assessment comes from asking patients about these distinct, yet often correlated areas of function and well-being.

There is general consensus that key domains of HRQoL include *physical*, *functional*, *emotional*, and *social/family* well-being [24]. Physical well-being refers to perceived and observed bodily function or disruption and includes symptoms such as pain, fatigue, and nausea. Functional well-being refers to one's ability to perform the activities related to one's personal needs, ambitions, or social role and includes things like ability to work, sleep, and enjoy life. Emotional well-being covers positive and negative affect as well as life enjoyment and appreciation. Social/family well-being includes a broader range of perceived support, leisure activities, family well-being, and intimacy. Over time, this framework has expanded to include additional targeted domains such as disease-specific symptoms and treatment side effects for more comprehensive and clinically relevant assessment (Fig. 6.1).

6.2.2 Patient-Centered Development

Centered on these domains and early results based on several hundred people diagnosed with cancer, the Functional Assessment of Cancer Therapy-General (FACT-G) quality-of-life questionnaire was published in 1993 [25]. It was designed as the core measure for a larger measurement system that enables researchers and clinicians to add relevant subscales for more targeted assessment of disease-specific or treatment-specific assessment. Version 4 of the FACT-G is comprised of 27 items and serves as a global measure of cancer-related HRQoL. It was developed with input from patients via qualitative methods and has undergone extensive validity testing with demonstrated relevance across cancer subtypes [23, 26–29]. To address the need for more targeted assessment, "additional concerns" subscales were developed, each to assess the unique symptoms and sequelae associated with a given diagnosis (e.g., prostate cancer), condition (e.g., anemia), or treatment effects (e.g., neurotoxicity; bone marrow transplant). Additional concerns subscales are combined with the core FACT-G and then named for the subscale's content (e.g., FACT-G + Breast cancer additional concerns subscale = FACT-Breast, or

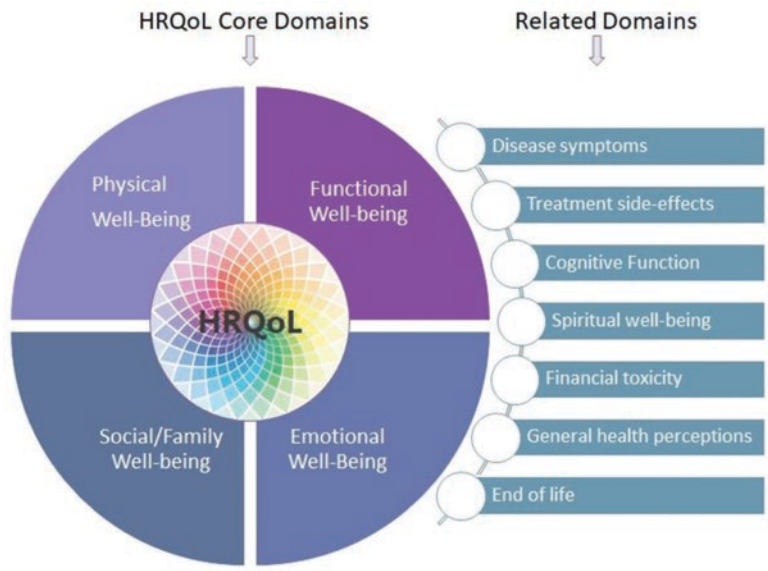

Fig. 6.1 HRQoL conceptual framework

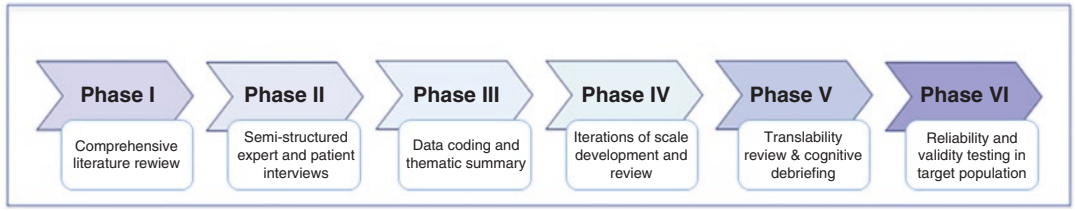

Fig. 6.2 FACIT Measure Development Process

FACT-B). Qualitative and quantitative methods used in the development and initial validation of the FACT-G served as a prototype for future scale development which is both patient-centered and comprehensive. Over time, the measurement system has expanded to cover other chronic illness conditions such as multiple sclerosis and HIV disease and to more targeted disease-related symptom assessment via brief symptom indexes.

The standard process for FACIT measure development includes phases of data and information collection (literature review, interviews with patient and clinicians) and data summaries followed by iterations of content/item development and expert review (Fig. 6.2). After a draft measure is developed, it undergoes a translatability review and cognitive debriefing with patients, and then is revised as needed.

The use of qualitative techniques in particular, such as concept elicitation via semi-structured interviews with purposefully selected patient populations [30], is a critical standard used to ensure patient-centered measure development for all FACIT scales. These methods utilize direct patient-input to better understand symptom experience and impact, as well as the associated social, emotional, and functional sequelae. Using semi-structured interview guides, trained interviewers solicit open-ended input about the patient experience, followed by targeted probing to help confirm and frame identified issues. Then, applying a constant-comparative approach [31], data are coded, summarized thematically, and used to identify priority concerns for measure content, typically guided by input from clinicians and the literature. Patient descriptions of unique symptomatology (such as "flushing episodes" in patients with carcinoid syndrome due to a neuroendocrine tumor) are often instrumental in writing or selecting items that best capture symptom experience. Once a measure has been developed, a translatability assessment is conducted [32] by a language translation specialist. This is to help identify items that may pose conceptual or semantic challenges either within- or across languages or cultures when undergoing multilingual translation. Use of cognitive debriefing interviews with patients ensures initial content validity, including that it comprehensively captures the most clinically relevant concerns, and that items are relevant and understandable as written [30]. Further testing is done in the target population to evaluate reliability and validity, including responsiveness to change.

6.2.3 Scope of Measurement System

Today, the FACIT system consists of over 100 distinct self-reported questionnaires that assess a wide variety of diseases, symptoms, functional abilities, general perceptions of health and well-being, and other aspects of health-related quality of life such as cognitive functioning and spirituality. Collectively there are approximately 700 unique items appropriate for use with adults aged 18 and older, and another 130+ items appropriate for use in children aged 8–18 (Fig. 6.3). Most FACIT items have interview-demonstrated face and content validity, and all were created with direct input from patients and expert clinicians.

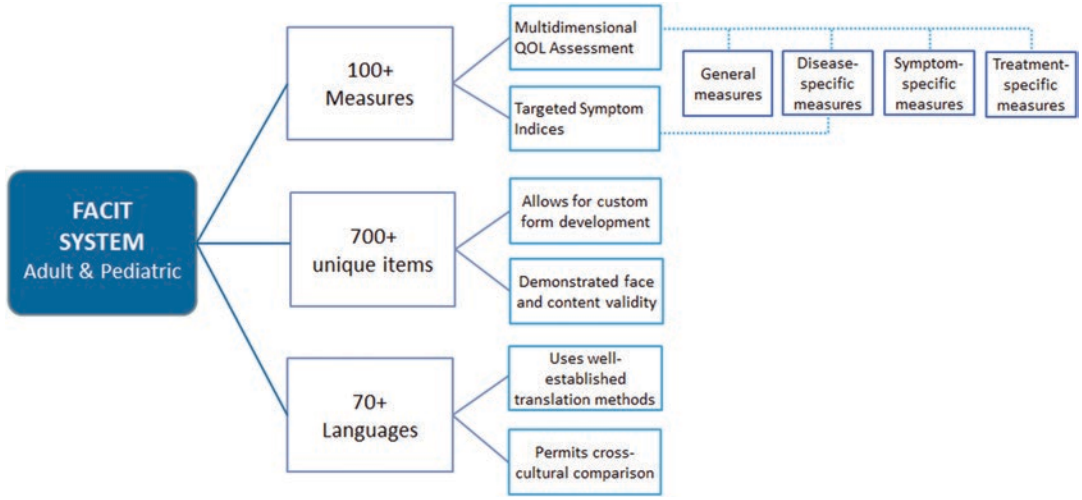

Fig. 6.3 FACIT Measurement System

6.2.4 Translations/Universal Translation Approach

Increasing use of PROs and the globalization of clinical trial research has created an ever-growing need for multilingual translations to permit multinational data pooling and cross-cultural comparisons. The multilingual translation methodology for FACIT measures was first published in 1996 [33] and has since been refined in keeping with translation and health sciences industry standards [7, 34, 35]. The context of patient-reported health which includes the assessment of physical, functional, social, and emotional symptoms adds an additional level of complexity, making this translation process highly specialized and nuanced. The primary goal is to achieve conceptual or semantic equivalence (vs a literal translation) such that the translation reflects both the denotative and the connotative meaning [36].

The current FACIT translation and linguistic validation methodology adheres to a multi-phase process and uses linguistic specialists who understand the unique needs of PRO assessment translation [35]. This includes the following steps: (1) an initial translatability assessment phase (assisted by the use of an evolving dictionary of concept definitions for FACIT items); (2) independently conducted forward translations from the source language to the target language by two linguists; (3) a review and reconciliation of the forward translations; (4) a back-translation by a certified translator who is a native speaker of the target language; and (5) review and harmonization with other translations as necessary. The FACIT translation methodology ensures that all translations undergo linguistic validation with patients in appropriate countries. In this process, native speaking patients of the target language answer the translated questionnaire and then participate in a cognitive debriefing interview during which the meaning, understandability, and cultural relevance of each translated item is assessed. The data are carefully reviewed by trained personnel to ensure that the final translation is semantically, culturally, and linguistic appropriate, and as equivalent to the source language version as possible.

The FACIT translation methodology, adopted by the HealthMeasures family of measurement systems (Patient-Reported Outcomes Measurement Information System (PROMIS®) [37]; Quality of Life in Neurological Disorders (Neuro-QoL) [7]; NIH Toolbox [7]), emphasizes a "universal" translation approach so that there is a single valid translation for each language, designed to work across different countries that speak the same language [7, 35, 38]. The universal approach provides several advantages to a

country-specific approach that produces multiple same-language versions across different countries. These advantages include the following: (1) enables language subgroup comparison, without requiring a check on bias introduced by different translations (e.g., comparing Spanish-speaking groups in the United States to one another or to people in Spain or Latin America); (2) minimizes bias introduced by multiple, country-specific translations in a project or trial; (3) simplifies logistics and analysis of multinational clinical trials; and (4) facilitates survey administration in the case of migrating populations [7]. In cases requiring a universal translation, the standard methodology is modified during the translation and review steps and in cognitive debriefing to include native linguists from each relevant country.

6.3 Structure

The original FACIT questionnaire structure is based on multidimensional assessment of general HRQoL which includes domains (subscales) of physical, functional, social/family, and emotional well-being, each scored separately and summed to a total score. Each subscale has 6–7 unique items that address common symptoms and concerns of patients with cancer, regardless of type (e.g., I have pain, I feel nervous, I am able to enjoy life); Version 4 of the FACT-G is 27-items. When "Additional Concerns" subscales are included for added specificity, they appear at the end of the general measure, as a fifth subscale.

6.3.1 Rating Scale

Rating scales are a critical component of a PRO's ability to accurately and reliably assess intended outcomes. While there are no clear standards on what comprises an optimal rating scale in terms of format and number of response categories, there is general consensus that response options should be distinct (i.e., categories that patients can easily distinguish), clearly written, appropriate for the targeted population, well labeled, present a "clear progression" or hierarchy of concept, cover the full range of the experience in even increments without gaps, and be a sensible fit with the questions being asked [4, 39, 40].

A Likert scale is well suited for patient-endorsed symptom burden and other patient-rated outcomes that typically assess symptom frequency or intensity. By design, they are ordinal scales that use a series of fixed choices to measure incremental levels of endorsement, and assume that the nature of the experience being measured is linear [41, 42]. The scale therefore inherently ensures incremental and progressive coverage of the full range of the symptom experience (such as with "not at all" to "very much"). Research critically evaluating rating scales in patient-reported outcomes using Rasch scaling techniques has demonstrated that complicated question format, a large number of response categories, or unlabeled categories tend to pose challenges [40]. A fairly large body of research has concluded that the optimal number of response options is between four and seven [43]. A greater number of options can lead to cognitive burden and reduced distinction between adjacent response options, sometimes producing a lack of monotonic relationship between response option and severity of what is being assessed. On the other hand, fewer than four response options may not sufficiently capture the range of experience, may fail to differentiate people from one another, and can increase the risk floor or ceiling effects [39].

FACIT Measures use a 5-point Likert-type response scale labeled 0 = Not at all; 1 = A little bit; 2 = Somewhat; 3 = Quite a bit; 4 = Very much. The wording is simple and unambiguous. These response options were selected based on piloting options with cancer patients in the initial development of the core FACT-G measure [25] and again in many subsequent investigations via cognitive interviewing and statistical exploration. Based on cognitive interviewing in the PROMIS initiative, patients confirmed comprehension of these response options, as well as their ability to differentiate between response categories [39].

6.3.2 Recall Period

FACIT measures use a 7-day recall period and the following introductory instruction: "*Below is a list of statements that other people with your illness have said are important. Please circle or mark one number per line to indicate your response as it applies to the past 7 days.*" Recall periods vary widely across the full spectrum of HRQoL questionnaires, from "right now" assessments through daily, weekly, and monthly time frames. The 7-day option is most common among oncology questionnaires, probably because shorter intervals provide an insufficient period of time to experience the range of content sampled in the questionnaire, and yet longer periods of time become increasingly difficult to recall accurately. Symptom-only measures often use daily (24-h or end-of-day) recall, especially if attempting to measure symptom improvement or worsening over a brief period of time. Much attention is paid to recall period, despite any evidence that it has a significant effect on responses [44]. In fact, qualitative studies suggest that many respondents neglect, forget, or replace the instrument-defined recall period when completing questionnaires [45]. In addition, there is evidence that the same questions administered with no recall period, 24-h recall, and 7-day recall, produce the same result [42]. Similar results comparing 7-day and 4-week recall also exist [46].

6.3.3 Mode of Administration

Ideally, FACIT questionnaires are self-administered. The original FACIT measure administration was via paper format, and most of the early measures were validated in the context of self-report via paper forms. Interviewer administration (in-person and by telephone) has also been used with success when conducted by someone trained in non-biasing interview techniques [47]. More recently, advances in technology have enabled electronic methods for PRO administration, including by telephone using interactive voice response (IVR), and via touchscreen, computer tablet, and smartphones using web-based platforms that enable electronic data collection and storage [47–49]. Research comparing mode of administration for health outcome measures (paper and pencil vs. computer-based assessments), including FACIT measures, has demonstrated a high degree of equivalence across a variety of patient populations and clinical settings [50–52]. In addition, a systematic review by Meirte and colleagues (2020) provides convincing evidence that ePRO administration offers many advantages over form administration, including patient preference and acceptability, cost, shorter completion time, data quality, response rates, and improved symptom management / health communication. Disadvantages include a higher upfront investment in equipment and technology services and challenges faced by people with low-computer literacy [53].

6.3.4 Scoring

For all FACIT measures, higher scores are better than lower scores. This is true whether measuring a symptom or a functional ability. All FACIT measures use raw total scoring approach without subsequent transformation. Scoring recommendations permit for a variety of component and composite calculations, depending on the desired outcome assessment, meeting FDA guidance recommendations for both global and targeted symptom evaluation. For any FACIT measure, subscale scores are calculated by first reversing negatively stated-items (subtracting the response from "4") and then summing the raw (0–4) scores. A total score is then derived by summing subscale scores. Alternatively, the sum of the physical well-being, functional well-being, and "additional concerns" subscales will yield a "Trial Outcome Index" (TOI) which is often used as a single primary clinical trial endpoint, because it allows for more targeted symptom assessment. If there are missing items, subscale scores can be prorated. This is done by multiplying the sum of the subscale by the number of items in the subscale, then dividing by the number of items actually answered. When there are missing data,

prorating by subscale in this way is acceptable as long as more than 50% of the items were answered (e.g., a minimum of 4 of 7 items, 4 of 6 items). The total score is then calculated as the sum of the un-weighted subscale scores. The scale score is considered to be an acceptable indicator of patient quality of life as long as greater than 50% of items are answered. In addition, a total score should only be calculated if ALL of the component subscales have valid scores. Multilingual versions can be scored using the English language scoring guides.

6.3.5 Symptom Indexes

While multidimensional assessment is the standard for measures of health-related quality of life, recent PRO trends in clinical trial investigations have moved toward more focused evaluations of symptoms and function. The catalyst for this shift comes from the 2009 United States Food and Drug Administration (FDA) draft guidance which called for targeted oncology trial endpoint assessment, recognizing that domains of HRQoL such as social and emotional well-being may not be as immediately responsive to treatment [4]. This created the need for brief, validated, clinically relevant PRO measures that focus on priority symptoms [54]. To meet this need, Cella and colleagues [55, 56] adopted recommendations to create a series of disease-specific symptom indexes for targeted endpoint assessments [56, 57]. Building on existing questionnaires in the FACIT Measurement System [23, 58, 59] that had previously undergone extensive patient-centered development and validity testing, 11 tumor-specific symptom indexes (bladder, brain, breast, colorectal, head and neck, hepatobiliary, kidney, lung, lymphoma, ovarian, and prostate) were derived [60–69]. FACIT symptom indexes are validated, abbreviated measures that include patient- and clinician-endorsed priority symptoms, function and treatment side effects associated with the specified condition, promoting patient-centered outcomes suitable for clinical and regulatory purposes.

6.3.6 Item Library and Custom Forms

FACIT is a commonly used measurement system in oncology, providing comprehensive, multidimensional measurement of HRQoL. Recently, Basch and colleagues developed the Patient-Reported Outcomes-Common Terminology Criteria for Adverse Events (PRO-CTCAE™) measurement system, a compendium of PRO items uniquely targeted to the assessment of symptomatic treatment-related toxicities in oncology care [70]. PRO-CTCAE is novel in that it allows for the assembling of individually selected questions drawn from a much larger pool of items (100+), advancing the acceptability of customizable forms and use of individual items. In keeping with this conceptual and structural approach to PRO assessment, FACIT has recently developed a comprehensive item library (FACIT Item Library; https://wizard.facit.org) which enables selective assessment of items or subsets of items for specific use. Item libraries are also able to accommodate new content in order to stay current with the changing landscape of cancer treatment. The FACIT item library includes over 700 unique health-related PRO items that assess a wide variety of disease- and treatment-related symptoms, functional abilities (physical, mental, social), general perceptions of health and well-being, and other aspects of health-related quality of life. Most items have demonstrated face and content validity, and many have been translated in over 70 languages. The benefit of custom form development includes highly targeted assessment options, while limiting assessment burden.

6.4 Interpretation

There are multiple sources of materials and research that can help interpret PRO scores, and this is true of FACIT instruments as well. The FACIT website (www.facit.org) is the best option for comprehensive advice on interpreting FACIT measures. Available resources for interpretation include reference or normative values, anchor

variables, published information on important group differences and important change for groups, and responder definitions at the individual level. Below, we detail the available evidence for FACIT instruments in each of these areas. We also recommend and demonstrate useful methods for identifying meaningful and clinically important difference and change.

6.4.1 Reference Groups

Reference values are population values of a PRO instrument. The population can be a particular disease population or the general population. They are also often useful if generated for a particular political or geographical designation, e.g., at the country level. Such values can be useful for putting scores of an individual or group into context. Typically, reference values include averages, dispersion (e.g., standard deviation), ranges, or other aspects of the scores' distributions. They are often reported for an overall sample and for key demographic groups (e.g., by age and sex). Reference values are most useful if they are estimated using a representative sample of patients, regardless of whether that is for the general population or a particular disease sample. Reference values can be applied usefully in both research and clinical settings.

There have been multiple reports of reference values for FACIT instruments. These include values for cancer populations [71] and for the general population [72, 73]. For the FACT-G total score and subscales, two US-based studies have estimated reference values for the FACT-G and subscales for adult cancer populations [71, 72], and one of these studies estimated reference values for the US general population. In addition, an Austrian study estimated reference values for the Austrian general population [74]. Table 6.1 shows the normative values from these studies. The values for the adult cancer populations are very similar, providing additional confidence in them.

In addition to the FACT-G instrument, reference values have been published for the FACT-General Population (FACT-GP; general population sample) [75, 76]; FACT Kidney Symptom Index instruments (FKSI; general population sample) [73]; FACIT-Fatigue (general population sample) [77–79]; FACT-Cognitive Function (FACT-Cog; healthy population) [80, 81]; and the FACIT-Spiritual Wellbeing Scale (FACIT-Sp-12) [82]. We recommend that these reference values be used for comparison to scores from future research.

6.4.2 Clinical and Other Anchors

Anchor variables are very useful tools to help interpret FACIT score differences and change. Anchors are external criterion variables on which the magnitude of change on the construct of interest is well-understood [83, 84] and therefore can be used to "anchor" an interpretation of difference or change on the PRO of interest. Anchors are useful for multiple important applications in PRO-based research. First, anchors are used to test known-groups validity and responsiveness to change [85] in the process of establishing a PRO's psychometric properties. Second, and more germane to the interpretation of FACIT measures, there is now general consensus that anchor-based approaches are most appropriate for establishing thresholds for important differences and important changes at the group level. In this case, "differences" refer to cross-sectional, between-groups comparisons, and "changes" refer to within-group comparisons over time. Finally, anchoring PROs to clinically familiar differences and changes can help translate their meaning to patients and clinicians [84].

Multiple types of anchors are useful for establishing important differences and changes. There is significant focus on patient-reported anchors [86]. Patient-reported anchors have the advantage of utilizing the same assessment method, and they typically assess changes that are meaningful to patients. In addition, when the patient-reported anchor represents the same construct as the PRO of interest, we have more confidence that the difference or change estimates derived from an analysis using the anchor are relevant to the PRO [86]. However, other types of anchors may be

Table 6.1 Reference values for FACT-G and subscales in adults with cancer and general population

	Brucker et al. (2005) [72]		Pearman et al. (2014) [71]	Holzner et al. (2004) [74][a]
	General population (N = 1075)	Cancer (N = 2236)	Cancer (N = 5065)	General population (N = 926)
	Mean (SD)	Mean (SD)	Mean (SD)	Mean (SD)
PWB	22.7 (5.4)	21.3 (6.0)	21.0 (6.0)	24.9 (4.1)
SWB	19.1 (6.8)	22.1 (5.3)	22.0 (5.3)	20.2 (5.8)
EWB	19.9 (4.8)	18.7 (4.5)	18.1 (4.6)	19.5 (4.5)
FWB	18.5 (6.8)	18.9 (6.8)	18.2 (6.6)	21.4 (5.5)
FACT-G	80.1 (18.1)	80.9 (17.0)	79.3 (17.0)	86.5 (15.2)

PWB Physical well-being, *SWB* Social well-being, *EWB* Emotional well-being, *FWB* Functional well-being, *FACT-G* Functional Assessment of Cancer Therapy – General
[a]German version of the FACT-G

useful as well, especially in cancer research [87]. For example, clinical variables that are not the same construct as the PRO but have a demonstrable relationship with the PRO, such as adverse events, tumor response, or progression [88], may be useful as well. However, any anchor used should be sufficiently correlated with the PRO to justify its use [87, 89].We require a minimum correlation of 0.30 to justify use of an anchor; although correlations above 0.40 are preferred, as we have noted a paradox by which anchors with lower correlations tend to produce smaller estimates of important difference or change. Because this is essentially an exercise in acquiring multiple converging points of evidence, we advise use of multiple anchors that include patient report, clinician report, and objective clinical metrics (e.g., laboratory values; radiographic data).

Table 6.2 lists some examples of key anchors that can be considered for use with FACIT instruments. This list of anchors is non-exhaustive, and there are other appropriate anchors that investigators may find useful for underpinning important differences and changes.

6.4.3 Important Differences and Change

At the group level, determining the level of difference that is considered important to patients or other stakeholders over and above statistical significance can enhance interpretation because, with large sample sizes, even trivial differences can be statistically significant [100]. Important difference estimates can be used to determine whether patient groups differ in HRQoL, and may be especially useful for planning future studies by providing a basis for power analyses. Similarly, important change estimates can

Table 6.2 Examples of anchors for estimating group-level important differences and changes

Anchor	Source variable	Reporter/data source	Determines important difference or change	Examples of use in FACIT
PRO with established important difference threshold	Baseline or other cross-sectional PRO assessment	Patient	Difference	Salsman et al. [90]; Rebelo et al. [91]
PRO with established important difference threshold	Baseline and post-baseline PRO assessments	Patient	Change	Garland et al. [92]; Peipert et al. [93]; Rebelo et al. [91]
Patient global impression of change	Baseline and post-baseline PRO assessments	Patient	Change	King et al. [94]
Difference in ECOG or other performance status rating categories (e.g., 0 vs. 1 vs. 2)	Baseline ECOG performance status rating	Patient or clinician	Difference	Yount et al. [95]; Salsman et al. [90]; Peipert et al. [93]; Cella et al. [96]
Change in ECOG or other performance status rating categories (e.g., increased one category vs. same)	Baseline and post-baseline ECOG performance status rating	Patient or clinician	Change	Yount et al. [95]
Number of adverse events ≥ grade 3	CTCAE, labs, PRO-CTCAE	Clinician, labs, patient	Difference	Peipert et al. [93]
Duration of progression free survival	Progression free survival endpoint	Clinician, medical test	Change	Cella et al. [97]
Tumor response category	RECIST categorization for clinical activity	Clinician, medical test	Change	Cella et al. [96]
Overall survival	Categorized length of survival	Clinician, medical record	Change	Cella et al. [98]; Steel et al. [99]

indicate the amount of change that patients find meaningful or that indicate clinically important improvements or decrements.

A previous summary of important differences and changes on FACIT instruments found relative consistency in the magnitude important differences in terms of proportion of the total scale points [87]. In summary, the following ranges for important differences were found: FACT-G Total: 4–7% of total scores (3–7 units), FACT-G subscales: 7–11% (2–3 units), symptom-targeted instrument totals (e.g., Total FACT-Anemia, Total FACT-Breast, Total FACT-Colorectal, Total FACT-Head and Neck): 4–8% (5–12 units), and trial outcome indexes (e.g., Fatigue, Anemia, Biological Response Modifiers, Breast, Colorectal, Lung): 5–7% (4–7 units). This was a thorough aggregation of data up to 2005, but many studies estimating important differences for FACIT instruments, especially newer instruments or for non-cancer populations, have been published since that time [91, 92, 101–103]. After collecting 15 additional years of data, these 2005 estimates have held true.

We recommend that researchers consult the literature and www.FACIT.org for up-to-date and appropriate important difference or change estimates for any given FACT or FACIT scale of interest. To implement this recommendation, it is important to use estimates of important change that have come from longitudinal studies actually focusing on change over time in the FACT or FACIT scale of interest, instead of substituting a cross-sectional estimate of the important difference where an estimate of important change is needed.

There are a few reasons to distinguish between change versus difference estimates. First, analyses to estimate important change typically use change scores (i.e., difference between baseline and a post-baseline follow-up), which may be distributed differently than FACT/FACIT scale scores at a single cross-sectional cut. Second, the analyses used to determine change often differ from analyses to estimate important differences in some ways. Identifying important changes in terms of meaningfulness to patients is required to support the use of FACT/FACIT instruments in regulatory applications. The FDA, for one, has prioritized estimating meaningful change thresholds for PROs using patient-reported anchors that measure the same construct or domain of the PRO to be used as an endpoint in trials to show treatment benefit [104]. A very common anchor for this kind of application is the patient global impression of change (PGIC), which retrospectively asks the patients how much they have changed on a domain of interest over a clinically relevant period of time and a set of discreet response options to characterize this change [105]. Then, the difference in mean PRO change scores can be examined over the PGIC response options to determine the amount of change on the PRO associated with meaningful categories as defined on the PGIC, e.g., difference in mean PRO change scores between patients reporting being "about the same" and "a little worse" on the PGIC anchor. To help interpret these differences, empirical cumulative distribution plots (eCDF) can be created and plotted to represent change on the PRO within each anchor category.

As an example, we utilized data from the Measuring Your Health (MYHealth) Study. The MYHealth Study was a population-based study that collected data on cancer patients from several Surveillance, Epidemiology, and End Results (SEER) registries. This dataset contains baseline surveys for 5513 cancer patients with multiple cancer types, across multiple cancer sites and distributions of demographic and clinical characteristics representative of the US cancer population. The sample characteristics of this study have been reported elsewhere [106, 107]. There was a 6-month follow-up survey on which the FACT PWB and a physical function-specific PGIC item was administered: "*Compared to six months ago, how is your physical function now… A lot better, A little better, About the same, A little worse, and A lot worse*." We drew a sample of 2867 patients who had non-missing data for the FACT PWB at both baseline and the 6-month surveys so that a change score could be created, and non-missing physical function PGIC. Since HRQoL decline is more common among cancer patients in the context of clinical studies, and little difference in physical function on a PRO is expected between

Table 6.3 Meaningful within and between group changes on PWB anchored to physical function PGIC

Physical function PGIC category	*N*	Mean	Difference[a]	Baseline SD	Effect size[a]	*p*-value[a]
Much worse	80	−4.4	–	5.96	–	–
A little worse	220	−2.1	−2.3		−0.39	<0.001
About the same	1268	0.3	−2.4		−0.40	<0.001
A little better/much better	1299	1.7	−1.4		−0.23	<0.001

[a]Derived from adjacent category differences: Much worse vs. A little worse, A little worse vs. About the same, About the same vs. A little better/Much better $F = 104.31$ (df = 3), $p < 0.001$

those reporting "A little better" and "A lot better" on the PGIC, these categories have been collapsed.

Table 6.3 shows differences in PWB change scores (baseline to 6 months) between the physical function PGIC categories. The correlation between the change score and the PGIC rating was −0.30, meeting our minimum criterion for proceeding. Statistical significance of the differences was tested using ANOVA for the overall table (F statistic) and between adjacent categories (least squares means). In addition, we computed an effect size for adjacent categories as the difference in mean change scores divided by the baseline standard deviation.

This approach, known widely as the "mean change" approach, is consistent with the FDA guidance. Examining Table 6.3, we would conclude that meaningful between group changes, quantified in terms of differences in the adjacent category PWB change score means, were in the range of 2–3 PWB points for deterioration (getting worse) and 1–2 points for improvement (getting better). To further interpret these differences, we also plotted eCDFs for the PWB change score at each level of the physical function PGIC anchor (Fig. 6.4). At each point on the plot, each curve represents the probability of achieving that value or lower change score on the PWB. The red line at 50% indicates the median change. These curves are useful for examining the separation in change scores for patients falling within the anchor categories, which in turn may reflect the PWB's ability to capture change in physical function. However, while helpful for understanding how well PRO responds to change, since it is at the group level, the mean change method and plotting eCDF curves across such anchor categories is not appropriate for identifying responder definitions [108, 109]. A more appropriate method for that is found in the next section.

There are some additional drawbacks and cautions around use of the mean change method, especially when retrospective, PGIC-type anchors are employed. One noted challenge with such items is their tendency to be more correlated with the second (follow-up) assessment than the change score or baseline, and therefore actually reflect current status at the time of PGIC assessment more than actual change [110]. In addition, if the follow-up period is long, there may be recall issues [111]. In the current example, these issues may have occurred. The PGIC was correlated with baseline PWB scores at only $r = -0.16$ while it was correlated with the 6-month PWB score at $r = -0.39$ (correlation with PWB change score was $r = -0.30$). Researchers should consider balancing the use of PGIC with other anchors. A useful alternative to the PGIC may be to examine prospective change in a similar item, the patient global impression of severity (PGIS), which assesses the level of symptom severity at a given time point.

6.4.4 Responder Definition

An important step in interpreting a PRO is to identify the responder definition, or the amount of change at the individual level that should be interpreted as treatment benefit [4]. Used alone, group-level estimates of change on PROs may not be appropriate for classifying individuals as having changed [109]. Identifying responders to treatment requires determining whether the change for an individual patient is significant, and group-level estimates of change (e.g., from important difference or change analyses) may

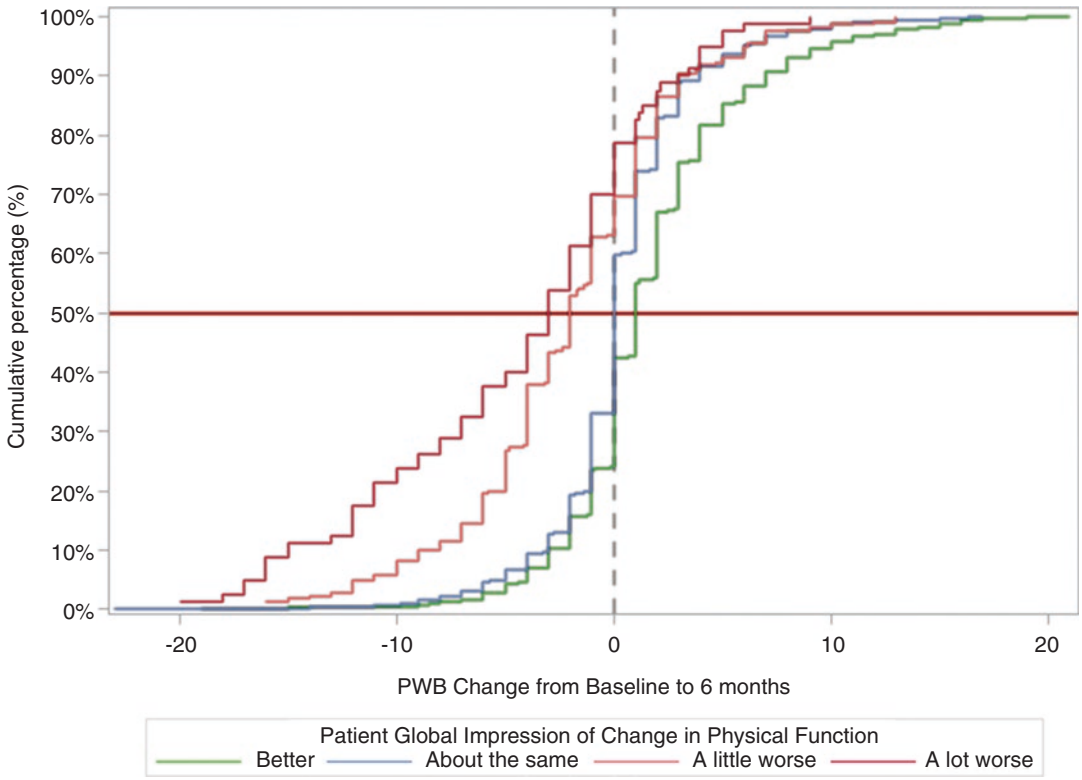

Fig. 6.4 eCDF curves for FACT PWB by categories of change on PGIC

under-estimate this [111]. This view is in contrast to current regulatory focus on defining responders in terms of meaningful change based on a patient-reported anchor [104]; such methods are necessarily group-based, focusing on identifying the average change for the group of individuals who said they changed on an anchor. In contrast to this approach, other authors have argued that, "a minimum standard for saying an individual has responded (improved) should include that the change in score is statistically significant [111]." Since it often requires large changes, statistically significant change at the individual level may also be meaningful to the individual [112, 113].

Methods like the reliable change index [114] can be used to determine the statistical significance of individual change. The RCI is calculated as:

$$\text{RCI} = X_2 - X_1 / \sqrt{2}\,\text{SEM},$$

where X_1 and X_2 are the individual patient's pre and post scores (e.g., baseline and follow-up cycle of assessment in a cancer trial). The SEM (standard error of measurement) is defined as the standard deviation of the baseline PRO score (SD_b) × (1-reliabilty)$^{1/2}$. The reliability can be obtained in various ways, though Cronbach's alpha or test-retest reliability may be the most readily available for most researchers. In most applications, if this RCI is larger than 1.96, the individual patient's change is considered statistically significant at $p < 0.05$. We refer to this threshold as RCI_{95}. For example, using RCI_{95}, each patient can be classified as having improved significantly ($RCI_{95} > 1.96$), did not change significantly ($-1.96 \leq RCI_{95} \leq 1.96$), or declined significantly ($RCI_{95} < -1.96$). This approach has recently been illustrated by Hays [115].

However, requiring 95% confidence that a patient has changed is not rational when the goal is *correct classification*. The logic of the RCI_{95} is to have 95% confidence that change has occurred,

so that then one can evaluate whether or not that change, reliably detected, is significant or meaningful. The magnitude of change for an individual required to be statistically significant is known to be large [113], and almost always exceeds group-based estimates of meaningful change by a good margin. Therefore, use of RCI_{95} risks incorrectly misclassifying a large number of changed individuals as unchanged. The probability of incorrectly classifying someone as changed is, on the other hand, vanishingly small, when the 95% CI is applied. These estimates may be larger than desired when attempting to accurately identify patients who have experienced a meaningful change, masking appreciable change among patients who do not meet the threshold required for 95% confidence. Therefore, instead of focusing on 95% confidence, reflecting statistical confidence, we propose a threshold that approaches more correct classifications of change versus no change. We suggest RCI thresholds at 70% or even 50% confidence level. To distinguish these thresholds, from the more conventional 90–95% thresholds used, we refer to these 50–70% confidence interval thresholds (RCI_{50}; RCI_{70}) as Likely Change Indexes (LCI), recognizing that this practice accepts some degree of measurement error.

To demonstrate an example, we used the MYHealth data described above. From this dataset, we drew a sample of 2941 patients with complete data for the FACT PWB at both baseline and the 6-month surveys. Using these data, we calculated the RCI_{95} for FACT PWB using the methods described above (RCI_{95}, critical value = 1.96). For comparison, we calculated RCI thresholds at the 70% (RCI_{70}, critical value = 1.04) and 50% (RCI_{50}, critical value = 0.67) confidence levels.

In these data, the baseline standard deviation was 5.95 and the coefficient alpha reliability was 0.90. Therefore, the SEM was 1.88. Using this information and the appropriate critical values, the minimum number of points change to be classified as significantly changed at the 95%, 70%, and 50% confidence levels were 5.22, 2.76, and 1.79, respectively. Figure 6.5 compares the proportion of individuals classified as having improved, not changed, and declined using RCI_{95}, RCI_{70}, and RCI_{50}. As can be seen in Fig. 6.5, a large majority (84%) of patients are classified as having not changed using RCI_{95}. Fewer patients were categorized as unchanged using RCI_{70}, and RCI_{50}, where 33% of the patients were classified as having improved and over 20% were classified as having declined (RCI_{50}).

In prospective randomized controlled trials, these RCI values can be used to compare the proportion of patients responding to treatment between the study arms. As an example, we plotted eCDF curves across arms from a hypothetical trial comparing the treatment benefit of a hypothetical cancer therapy to a placebo. The endpoint for this trial was the PWB, so treatment benefit is defined in terms of the number of PWB points increased. Figure 6.6 shows the eCDF for change in PWB stratified by study arm. Rounding up to the nearest integer, the RCI_{95}, RCI_{70}, and RCI_{50} thresholds indicate responder definitions of 6, 3, and 2 points, respectively. The vertical dashed lines in Fig. 6.6 show these responder definitions and can be used to compare the proportion of patients that would be categorized as responders to treatment between each arm. For example, at 2 points (corresponds to RCI_{50}), approximately 95% of patients in the active drug arm would be counted as responders, while only 75% would be counted as responders in the placebo arm. However, at 6 points (corresponds to RCI_{95}), just under 35% in the active drug arm would be classified as responders, while under 10% in the placebo arm would be classified as such. Examining these eCDF curves can help compare and contrast the plausibility of different responder definitions and narrow to a reasonable range of score change on the PRO that should be considered to define treatment benefit.

6.5 New Directions in Research and Clinical Practice

The FACIT Measurement System has been used extensively in research; not only in oncology but elsewhere, across scores of other diseases and health settings. Uses include clinical trials,

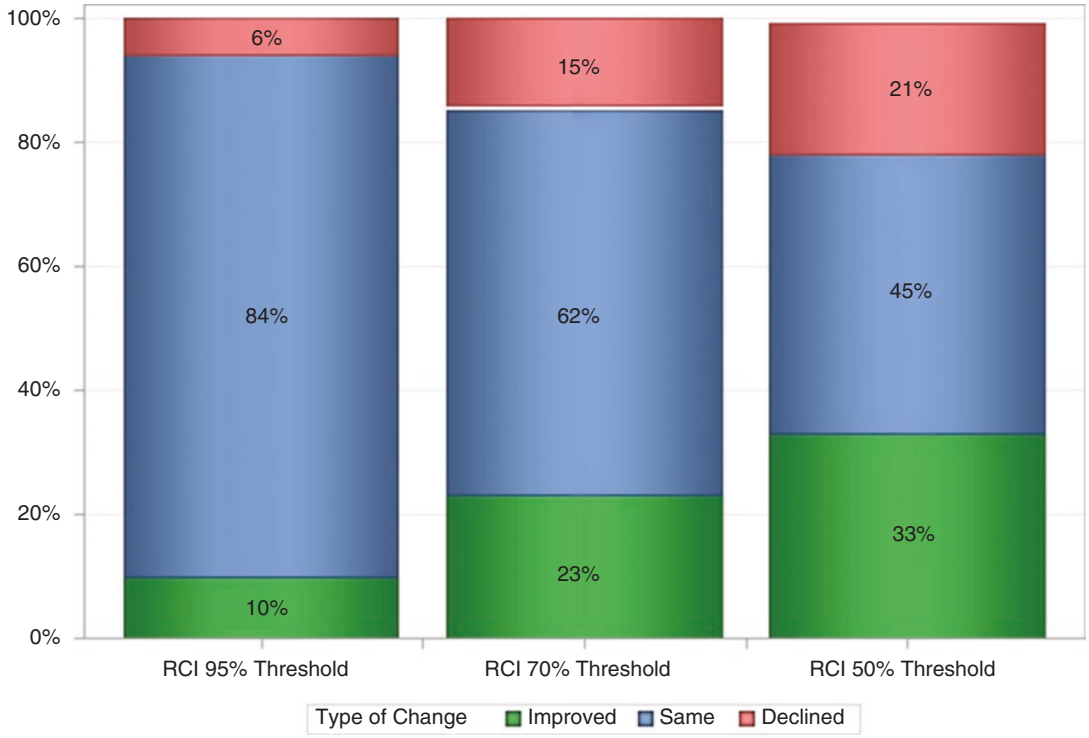

Fig. 6.5 Differences in responder categorization on FACT PWB using varying RCI thresholds

clinical practice research, descriptive studies, and investigations aimed to understand the burden of disease. Regulatory, clinical, and patient community interest in our research results, and their serious efforts to incorporate findings meaningfully into their evaluation of treatment benefit and harm, have created some pressure to simplify assessment and analysis. This often takes the form of shortening, modifying, and otherwise adapting our approaches to measurement, analysis, and interpretation.

At the same time, there has been increased interest in the use of FACIT measures in clinical practice. The goal of patient-centered care, aimed toward shared decision-making, is facilitated with the use of structured, formal assessment such as that offered by FACT and FACIT. However, as with research pressures, moving from methodological and clinical research into the clinical care arena has necessitated further modification of the structure of the FACIT Measurement System.

These recent trends have led us to create and make available the FACIT item library (described in Sect. 6.3). We now discuss two examples (one research; one clinical) of modifications and extensions made to accommodate the increased and welcome demand for practical, interpretable, and actionable use of FACIT. These are merely examples; many other similar activities are possible to consider.

6.5.1 Item GP5 and Treatment Tolerability

Over the past 30 years, the FACT-G has been included in hundreds of oncology clinical trials. One item in the Physical Well-being subscale is item GP5: "I am bothered by side effects of treatment." This item was included in the core questionnaire out of a realization that there are myriad side effects associated with cancer treatment, and the landscape of

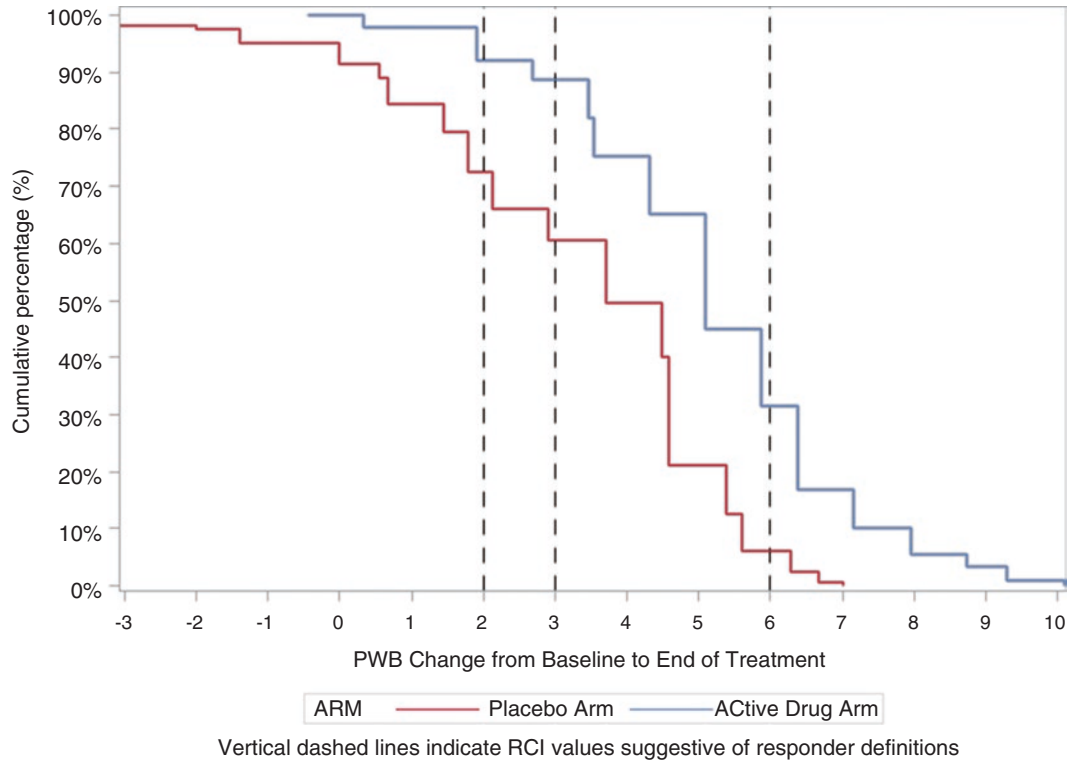

Fig. 6.6 eCDF curves for change in PWB from baseline to EOT stratified by arm

side-effect profiles is ever-changing. In most comparative clinical trials, there are multiple toxicities, and they differ in type and severity across treatment arms. One way to fairly compare treatments in a clinical trial is to obtain a straightforward patient rating of side effect bother. The US FDA and National Cancer Institute (NCI) have taken a keen interest in this GP5 item, as it provides a way to get a "bottom line" assessment from patients on clinical trials. We therefore make this question available, if requested, for use outside to the FACT-G questionnaire, and we have studied its validity as a single item. Our first few papers on this question in isolation demonstrated that it has validity as evidenced by its association with clinician-reported adverse events, treatment discontinuation, and other anchors [116–118]. Further work on the predictive power of this question, using baseline and change scores, is underway, funded by the NCI.

6.5.2 The FACT-G7: A Clinical Quality Tool

Clinical oncology practitioners, having become familiar with the FACIT Measurement System through their research participation, sought to use the FACT for monitoring patients in clinical care. Early attempts to use the entire 27-item FACT-G were promising, but ultimately perceived to be overly burdensome for the clinical setting. Equally important, many of the items were not felt to be clinically actionable. Parallel to these observations, in the United States, the American College of Surgery Commission on Cancer (CoC) issued a requirement that patients be monitored and treated for distress, as a condition of certification. This provided further motivation for brief, actionable assessment. This led us to a project to shorten the FACT-G to include only the very most important items to cancer patients. Fortunately, one of the seven very most important items was distress (worry), allowing a shortened

version to be used to fulfill the distress screening requirement and also get an assessment of pain, fatigue, nausea, and sleep. This led to the publishing of the "FACT-G-7," a 1-min measure with high correlation to the longer FACT-G, yet practical for clinical use [94, 119].

6.6 Conclusion

The FACIT Measurement System, which started from the FACT-G, a cancer-specific HRQoL questionnaire, is a collection of more than 100 measures of self-reported symptoms, functional status, and perceptions of distress and well-being, translated into over 70 languages. All of the measures are freely available for academic research (www.facit.org). The growth of the measurement system reflects the evolution of the HRQoL field over the past three decades, including the availability of an item library that affords countless opportunities for further research and clinical use.

6.7 Questions That Can Be Used for Learning/Testing

Question 1: Which of the following is not a component of health-related quality of life (HRQoL)?

(a) Symptoms of disease
(b) Side effect of disease
(c) Physical function
(d) Environment quality (e.g., air pollution)

Question 2: Which is more important in the multilingual translations of health-related quality of life (HRQoL) measures: the semantic or literal translation?

(a) Literal
(b) Semantic
(c) They are equally important
(d) Neither is important

Question 3: What is the FACIT-recommended approach for estimating important or meaningful differences and change?

(a) Distribution-based
(b) Anchor-based
(c) A combined distribution- and anchor-based approach

Question 4: How could you use reference values on patient-reported outcome measures like FACIT scales to help understand an individual patient's score?

Question 5: In your own words, how would you define an anchor measure, and how would you use it differently than a patient-reported outcome measure you are studying or applying in clinic?

Question 6: What approach would you take to understanding whether a group of patients has experienced a meaningful change on a FACIT scale? How would the approach differ for an individual patient?

6.8 A Topic for Discussion That Can Be Used in Teaching

Discuss the options for synthesizing clinical outcomes with health-related quality of life (HRQoL) outcomes in cancer research and practice.

6.9 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

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6.10 Research in Context

FACT-Derived Symptom Indexes

A collaboration with the pharmaceutical industry and the National Comprehensive Cancer Center Network (NCCN)

In 2006, following the release of the United States Food and Drug Administration (FDA) Draft Guidance for patient-reported outcome (PRO) instruments [1], and the experience of several FDA responses to pharmaceutical company submissions to

the FDA for PRO label claims, a collaboration between FACIT and the NCCN set out to reconfigure FACT questionnaires to be more "regulatory-friendly." Across several submissions of FACT questionnaires for regulatory review, some consistent themes emerged from FDA comments. These themes included issues related to content validity, documentation of early qualitative work previously conducted to develop FACT questionnaires, and the configuration of FACT subscales into terms such as "physical well-being," "functional well-being," "emotional well-being," and "total quality of life," labels that did not fit the FDA perspective on "well-defined" concepts. Working with colleagues at the National Comprehensive Cancer Network, FDA, and the pharmaceutical industry, the FACIT team developed a research protocol to modify and reconfigure 11 FACT cancer-specific questionnaires for regulatory use. This 5-year effort spanned two research projects across five NCCN institutions and a Chicago area community support organization.

Using methods consistent with the draft and final FDA Guidance [1, 2], we developed symptom indexes for patients *receiving chemotherapy for advanced cancer*. We narrowed the research context from the broader, more inclusive FACT context of any patient with cancer, at any point in the treatment trajectory. Using qualitative methods, both patients and clinician experts (physicians and nurses) provided input. Specific diagnoses included bladder, brain, breast, colorectal, head and neck, hepatobiliary, kidney, lung, lymphoma, ovarian, and prostate cancer. We created these symptom indexes to reflect the highest priority symptoms and concerns of patients with these 11 different cancers. Each index has three subscales: "*Disease-related symptoms," "Treatment side effects," and "Function/well-being*." These indexes, while designed for regulatory use, may also be of interest to clinicians and researchers seeking a briefer, more symptom-focused assessment of people with cancer compared to the longer, more inclusive parent FACT questionnaire. Typically, these indexes are less than half as long as the FACT questionnaire from which most (but not all) of their content was drawn. They are not meant to replace the FACT scales, but rather to provide an alternative. If one wishes to measure and score both the traditional FACT scales and the NCCN-FACT Symptom Indexes, simply add to the end of the traditional FACT questionnaire the items (typically 2–3) that are in the indexes but not included in the traditional FACT questionnaire. The NCCN/FACT Symptom Indexes, along with supporting peer-reviewed research papers, can be found at www.facit.org.

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7 Validating Cancer Quality of Life Assessment Tools: Psychometric Considerations

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Contents

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7.1 Introduction

This chapter introduces the different psychometric properties of a quality of life (QoL) instrument. An important stage in developing QoL questionnaire is to assess the psychometric properties of the new instrument, in order to produce validated and reliable results. These properties are numerous and are generally divided into three quality domains: the validity, the reliability, and the responsiveness. The choice of a QoL questionnaire in a study should be done according to these criteria of validation: Is the questionnaire validated for the population of interest? Is the questionnaire sensitive to the change related to the treatment the patient will receive? Is the questionnaire able to discriminate different patients' groups with expected difference in QoL level?

In this chapter, all these psychometric properties are defined. Then, the main statistical approaches recommended to assess each property are presented. Since each property must be studied with an appropriate sample size, some recommendations on minimum sample size requirement as well as empirical rules are provided. Finally, the interpretability, which is another important characteristic of QoL questionnaire while does not strictly belong to the psychometric properties, is defined with key elements to report. This chapter will enable the readers to: (1) be aware of all psychometric properties a QoL questionnaire should respect, (2) know which methods use to validate these properties, and (3) know how many patients are required for these analyses.

7.2 Definition of the Psychometric Properties of QoL Questionnaires

All instruments must satisfy psychometric properties. Each newly developed questionnaire should thus verify these properties. The questionnaire will then be validated for the population and the language of the validation study. These properties are numerous and are not all required to validate a questionnaire depending on the objective of the questionnaire developed. As example, if a scale has been developed to discriminate patients according to their health condition, then this scale does not need to be sensitive to QoL change over time.

Due to the heterogeneity in the taxonomy, terminology, and definitions of the psychometric properties, the COnsensus-based Standards for the selection of health Measurement INstruments (COSMIN) initiative proposed an international consensus for QoL questionnaires [1]. We followed this consensus in the presentation of the quality domains and subcategories. The definitions provided were sometimes reworded but we invite interested readers to read the paper presenting this consensus [1].

According to this consensus, the psychometrics properties that a QoL questionnaire must respect can be separated into three quality domains: the validity, the reliability, and the responsiveness.

7.2.1 Validity

The validity is the set of proofs certifying that the questionnaire really assesses what it is intended to measure and that it provides useful information to the expected objective. Since QoL is an unobservable variable, also called a *latent* trait by mathematicians, the objective is to be sure that the new instrument really assesses the QoL which can be quite difficult.

The validity domain includes three measurement properties: the content validity, the construct validity, and the criterion validity.

According to the COSMIN initiative, the content validity is the degree to which the content of a QoL instrument is an adequate reflection of the construct to be measured [1]. A good content validity is reached if all items within the QoL instrument are relevant, understandable, and exhaustive, with appropriate response categories and recall period. It is the most important psychometric property but also very challenging to evaluate. If some items are not relevant, it can bias the results of other psychometric properties

with, for example, an increase of the items' reliability [2]. Therefore, this should be the first measurement properties to assess.

Face validity, which belongs to the content validity, is the degree to which the items of a QoL instrument indeed appear to adequately reflect the construct to be measured. The face validity concerns the critical review of the items of a questionnaire after it has been developed, whereas the content validation is ensured during the questionnaire development. It entails to ask to the patients and the professionals to assess the relevance of the items, if they are comprehensive, redundant, or exhaustive, or if there is missing important information to the target construct. The instructions of the questionnaires as well as the recall period have also to be examined.

The acceptability of the questionnaire is also part of the content validity and insists to examine the acceptance of the questionnaire in terms of completion and the distribution of the items. More detailed information on content validity is provided in Chap. 4.

The construct validity is the ability of the instrument to assess what it is intended to measure. According to the COSMIN consensus initiative, the construct validity can be divided into three aspects, namely, the structural validity, hypotheses testing, and the cross-cultural validity.

The structural validity corresponds to the validation of the structure of the scale, that is, the number of dimensions assessed and the correspondence between the items and their dimensions. It is also defined by the COSMIN initiative as the degree to which the scores of a QoL instrument are an adequate reflection of the dimensionality of the construct to be measured [1]. This validity is only required for multidimensional scales, which correspond to the high majority of QoL scales in oncology due to the multidimensionality nature of QoL. It is an important process that should be done rigorously since this will induce which scores can be estimated.

The hypotheses testing regroups all hypotheses that can be made and includes convergent, divergent, and known-groups validities. The convergent validity aims to demonstrate that a given dimension of the new QoL instruments is highly correlated with other dimensions of external measure that theory suggests to be linked. Conversely, the divergent validity reflects that some dimensions of QoL are relatively unrelated to specific external domains. Convergent and divergent validities are generally assessed through different questionnaires. For example, dimensions of a questionnaire aiming to assess the information received by cancer patients will be expected to be highly correlated with those of a questionnaire assessing satisfaction with cancer care (reflecting convergent validity), but not with QoL dimension of another questionnaire (reflecting divergent validity) [3]. However, this property is sometimes assessed within the same questionnaire. In that case, the hypothesis is that an item within one subscale is highly correlated with other items from the same subscale and that is correlation is higher than those observed between the item and other subscales.

The known-group validity corresponds to the ability of the questionnaire to highlight difference in QoL scores between different groups of patients with expected difference in QoL level. For example, it seems coherent that depending of their disease stage, patients will not have the same level of QoL. We thus expected that patients with advanced cancer will have lower QoL level than those with localized cancer. The new developed QoL questionnaire should thus be able to highlight this difference. The known-group validity is thus the ability of the questionnaire to discriminate two groups or more of patients with expected difference in terms of QoL.

The cross-cultural validity is only required for existing scales we would like to validate in another language. A basic translation of the items in the new language is not enough to consider the questionnaire to be valid. The questionnaire should be adapted to the culture of the new language, items must be comprehensive and evaluate the same domain as in the original questionnaire [4, 5]. The definition provided by the COSMIN is the degree to which the performance of the items on a translated or culturally adapted QoL instrument are an adequate reflection of the performance of the items of the

original version of the QoL instrument [1]. This concept will be further explored in Chap. 12.

The criterion validity is the degree to which the new QoL questionnaire is an adequate reflection of an external criterion, such as a very well-known validated questionnaire, or the true value [1]. This property is generally divided into two components, namely, the concurrent and predictive validities, depending if the "gold standard" is assessed at the time of the QoL assessment or later.

Since QoL is not directly observable, the idea of the concurrent validity is to confront the QoL questionnaire to an existing and adequate "gold standard" assessing QoL. For example, if we developed a new QoL questionnaire specific to breast cancer patients, we need to compare our new questionnaire to another QoL questionnaire already existing and validated for breast cancer patients. This measurement property could only be assessed if another questionnaire is already available for our population. If such a scale is already existing, the necessity to develop a new one can be questionable. The new scale must give advantage to the former one. For example, it can be a shorter questionnaire, thus easier to use in clinical practice. The new scale can also be more specific of one domain of interest or of a subpopulation (e.g., specific to metastatic breast cancer patients).

The predictive validity is the ability of the QoL questionnaire to predict future health status or events, such as death or disease progression. In fact, QoL has been recognized as a prognostic value of overall survival in many cancer sites [6]. The occurrence of death could be a good event to predict in order to assess the predictive validity of the scale. However, as for all studies assessing overall survival, it can require a lot of time and patients to observe enough deaths depending on the cancer site and disease stage. Due to the longitudinal design required and this potential large interval time needed, the predictive validity is less often assessed than the concurrent validity as an indicator of criterion validity.

7.2.2 Reliability

The reliability corresponds to the ability of a scale to produce consistent and reproducible results. This includes three different psychometric properties, namely, the internal consistency, the reproducibility, and the measurement error.

For multi-item scales, all items from the same dimension must be consistent: it means that they should all measure the same concept. This property corresponds to the internal consistency, also called internal reliability, of a scale and is assessed through the analysis of the correlation among the items.

The concept of reproducibility, also called repeatability, refers to the ability of a scale to produce similar results between repeated measures when the patient remains in a stable health condition. This measurement property is also called reliability by the COSMIN initiative, but it can introduce a confusion with the reliability domain. This includes assessment repeated over time for the same patient (test-retest reliability) or, for example, by different raters (inter-rater reliability). Most of QoL questionnaires in oncology field are self-reported questionnaires; thus, the test-retest reliability is the target reproducibility assessed. However, we also briefly presented in next section the statistical methods to assess inter-rater reliability, useful, for example, in pediatric or palliative research. The test-retest reliability is important to be confident for the QoL results observed and to allow a clear interpretation of the results. In case of doubtful test-retest reliability, we could not guarantee that a change in QoL scores really reflects a change in QoL level. This property is not only required for QoL instruments, but also to general measure as, for example, blood measure.

Measurement error is defined as the systematic and random error of a patient's score that is not attributed to true changes in the construct to be measured [1]. The measurement error is a measure of the accuracy of the instrument. Any change above the measurement error will be considered as a real change.

7.2.3 Responsiveness

The responsiveness is the ability of a questionnaire to detect change over time in the QoL domain assessed [1]. The responsiveness property is linked to the reproducibility property and is often considered as part of the longitudinal validity. To assess this property, we thus need a longitudinal design. Repeated measures have to be done among patients experiencing a change in their health condition which could impact their QoL level. As an example, QoL can be assessed at diagnostic and just after surgery for newly diagnosed breast cancer patients. Researchers should guarantee that a not negligible proportion of the patients is likely to change, experiencing either deterioration or improvement, regarding the QoL instrument of interest.

7.3 Statistical Methods Used to Validate the Psychometric Properties

For each measurement property, the main statistical methods used are presented in this section. The cross-cultural validity is deeply presented in Chap. 12 and thus not presented in this section.

7.3.1 Content and Face Validity

As already mentioned, the content validity, including face validity, is mainly assessed through a qualitative judgment involving patients and professionals on relevance, clarity and exhaustiveness of the items, and the appropriateness of the response categories per item. The acceptability of the questionnaire by the patient is also useful at this stage. This is mainly evaluated through the percentage of missing response per item and the distribution of items. In particular, we are interested in possible significant floor or ceiling effect. A floor effect is defined as a high percentage of patients rating the lowest score on the scale. In contrast, a ceiling effect corresponds to a high proportion of patients with the highest score on the scale. Generally, a threshold of 15% is retained to consider the effect as significant [7]. If the floor or ceiling effect is thus greater than this threshold, it could indicate that either the item is not appropriated for the targeted population or the categories of response should be revised.

Researchers can then choose to retain or to delete some items if they do not respect all these key former criteria. As for the floor and ceiling effect, these criteria are mainly based on descriptive analysis. For example, we can have the following rules to keep the items:

- At least 60% of the interviewed patients considered the item as relevant.
- At least 60% of the interviewed patients considered the items as at least quite important.
- Less than 5% of missing data per item.
- Less than 15% of floor effect.
- Less than 15% of ceiling effect.

Items that do not respect one or more former criteria can thus be deleted or at least reworded. Other rules regarding items distribution can be made depending on the number of response category per item. Moreover, these rules can be adapted depending on the intended purpose of the questionnaire. For example, the European Organization for Research and Treatment of Cancer (EORTC) has proposed some guidelines to develop QoL questionnaire including decision rule to keep or to delete items [8]. These rules comprise criteria for item relevance and importance, and descriptive statistics. These thresholds were established for QoL questionnaires using a 4-point response scale per item ranging from "Not at all" to "Very much."

7.3.2 Structural Validity

The main statistical methods used and recommended to assess the structural validity are factor analysis and item response theory (IRT). Both can be used and are complementary.

Among factor analysis, there is a distinction between exploratory and confirmatory factor analyses (CFA). Exploratory factor analysis

(EFA) is recommended when there is no a priori information on the structure of the scale. The main objective of EFA is thus to identify the underlying structure of the scale and the relationship between the items while maximizing the variance explained. CFA is used when there are already hypotheses on the scale structure. The idea of the CFA is thus to confirm a priori hypotheses. Quality criteria are then examined in order to judge if the hypotheses can be considered as respected or not with enough statistical powerful depending on the sample size.

In QoL field, EFA is more often used than CFA. However, CFA is more powerful and is the recommended factor analysis method according to the COSMIN initiative in order to have a high-quality structural validity of the questionnaire. Thus, if an EFA has to be done because researchers do not have sufficient hypothesis on the underlying structure, it should be followed by a CFA on an independent sample. Generally, EFA is used at the early stage of questionnaire development. Then, a CFA is proposed on the latest version of the questionnaire to confirm the first hypotheses obtained using EFA.

Factor analysis is based on the correlation matrix of the items. The number of factors corresponds to the number of dimensions and thus to the number of scores for the scale. By default, in a statistical software, the maximum number of factors is equal to the number of items. However, the objective of this analysis is to extract a limited number of factors while explaining a high percentage of variance observed. The number of factors to retain is generally chosen according to the eigenvalues observed. For example, the widely used Kaiser-Guttman rule intends to retain all factors with an eigenvalue greater than one [9]. The eigenvalue obtained for a given factor represents the amount of variation in the data which is explained by the corresponding factor. The higher the eigenvalue, the higher the variance explained by the corresponding factor. In order to assess the validity of the structure, the total percentage of variance explained by the number of factors retained is generally reported. This total should be as high as possible. The percentage of variance explained by each factor corresponds to the eigenvalue divided by the total number of items.

The factor loadings are then studied. It is the correlation of the item with the identified factor. The item will then be assigned to one factor if its correlation to the corresponding factor is high and higher than its correlation observed with all other factors. A correlation of at least 0.30 can be used to consider that the item is at least moderately correlated to a given factor. If an item did not show at least a moderate correlation with any factor, the factor analysis should be computed again without this item. All retained items should be correlated with only one factor.

An important factor to consider while conducting EFA is that the solution proposed by default in any statistical software is not the unique one. Variation in the decomposition of the factors can be observed depending on the way to conceptualize and represent the factors. For example, the initial solution proposed by the model can be difficult to interpret and need a rotation of the factors. Two types of rotations are widely used, namely, the varimax rotation and the oblimin rotation. The varimax rotation aims to maximize the percentage of variance explained by the first identified factors. It induces that each factor is independent from each other. Thus, the factors are assumed to be unrelated. This is clearly an unrealistic assumption for most of multidimensional QoL questionnaires. In contrast, the oblimin rotation, or all other oblique rotations, allows the factors to be correlated. This second type of rotation is thus more suitable for most of QoL questionnaires.

For CFA, many criteria exist to assess if the model fit well the data. The recommendations are to report at least the chi-square test, the Root Mean Square Error of Approximation (RMSEA), the comparative fit index (CFI) or any comparable index, and the Standardized Root Mean Square residual (SRMR) [10]. The RMSEA analyzed the discrepancy between the hypothesized model and the data observed using the covariance matrix [11]. The RMSEA coefficient ranges from 0 to 1, with a high value reflecting a poor model fit. The SRMR is the square root of the difference between the residuals of the covariance matrix of

the observed data and the hypothesized model. The SRMR value ranges from 0 to 1, with a high value reflecting a poor model fit. The CFI also analyzed the discrepancy between the hypothesized model and the data observed, but it has the advantage to be not very sensitive to the sample size. CFI coefficient varies from 0 to 1, with a high value reflecting a good model fit. The COSMIN recommends the following thresholds to consider a high model fit: a CFI or comparable index >0.95, an RMSEA <0.06, or an SRMR <0.08. These criteria must thus be reported in the publication of the validation scale.

IRT models are also more and more used for questionnaire development and validation [12]. They can be useful for both validation of a questionnaire or to develop a shorter version of an existing questionnaire [13]. IRT models are based on the response to items themselves and not on the scores generated. The theory of these models is that the response the patient will provide to one item will depend on the true unobservable patients' QoL level (e.g., the latent trait) but also to parameters of the items. Two parameters are generally considered for QoL questionnaires: the item difficulty and item discrimination parameters. For dichotomous items (i.e., items with two responses categories (Yes/No)), the item difficulty parameter corresponds to the probability a patient will choose the response "Yes" to the item. The more the item is difficult, the less patients will choose the response "Yes" to this item. For ordinal response scales, parameters of response category difficulty are estimated per item. For example, the difficulty parameter for the response category j corresponds to level of latent trait the patient's need to reach to choose with equal chance the response category j or the next category $j + 1$. The item discrimination parameter corresponds to the ability of the items to discriminate patients with different underlying QoL level. IRT models include at least the item difficulty parameters. In that case, the discrimination is supposed to be equal across items.

Two families of IRT models are mainly used: the Rasch-family models and the Lord family models. The Rasch family models require the data to adapt to the models. In contrast, the principle of the Lord family models is to adapt as much as possible the model to the data observed. Indeed, all Rasch models assumed that the discrimination is equal across items while the discrimination can vary among Lord models. All these models are based on logistic regression model to represent the association between the patient's response to a given item and the patient's underlying QoL level.

Most of IRT models are based on three fundamental assumptions:

- The unidimensionality of the latent trait, that is, all items measure the same QoL component.
- The monotonicity, that is, the probability to choose a positive answer (the second response category) or at least a positive answer increase with the value of the underlying QoL level.
- The local independence, that is, the responses provided to one item must be independent of the response provided to all other items of the scale. Therefore, the order of completion of the items should have no impact on the responses provided.

These assumptions should be tested to confirm that the model chosen is appropriate and that results can be interpretable. Multidimensional IRT models exist but remain few used to date.

Among the Rasch models, the following models are the most used:

- The Rasch model [14], adapted for dichotomous items.
- The Partial Credit Model (PCM) [15], adapted for items on ordinal response scale with multiple categories of responses.
- The Rating Scale Model (RSM) [16], adapted for items on ordinal response scale with equal number of response categories for all items.

Since most of QoL questionnaire in oncology contains items on an ordinal response scale, the PCM or RSM models are more suitable than the Rasch model.

In order to validate the model retained, the adjustment of the data to the model should be

examined. As for CFA, the adjustment of the model could be expressed by the chi-square test, and other estimation like the RMSEA and CFI. The residual statistic per item should also be examined. If the standardized value for a given item is outside the range ±2.5, the corresponding item is susceptible to misfit the model. Abnormal high positive residual could be an indication of differential item functioning (DIF). A DIF occurs when one item does not reflect the same meaning for all patients. In contrast, abnormal low negative residual could reflect redundant items. DIFs are of particular importance in cross-cultural validity. IRT models are thus useful to validate the structure of the questionnaire and can be useful also for cross-cultural validity in order to check if items are understood in the same manner in all cultures.

7.3.3 Convergent and Divergent Validity

One method used to study the convergent and divergent validity is the multitrait-multimethod analysis. This method aims to estimate the correlation of each scale of the new developed QoL questionnaire with those of external measure(s) for which certain dimensions are supposed to be highly correlated with the QoL questionnaire of interest (convergent validity); and other dimensions are not supposed to be correlated with the QoL questionnaire of interest (divergent validity). The notion of *multitrait* refers to the multidimensionality of the scale. The multimethod is a reference to the multiple questionnaires used. In this method, the analysis is done on the scores computed for each scale. It needs to define a threshold to consider a correlation as to be significant or not. Generally, a correlation of at least 0.40 is considered as a moderate correlation.

Occasionally, researchers used this method within the QoL questionnaire of interest. This refers to the multitrait analysis. This could be controversial because it only assesses the convergent and divergent validity of the scale itself. This should not be used to validate the structure of the questionnaire in replacement of CFA as example. In this analysis, the convergent validity of the item is estimated through the correlation between one item and the score of its own dimension excluding the corresponding item. By contrast, the divergent validity of the item is estimated with the correlation of the item with the score obtained for all other dimensions of the questionnaire. The correlation of the item should be higher with its own score dimension than those observed for all other dimensions.

7.3.4 Known-Groups Comparison

The known-groups validity aims to compare the QoL level of different groups of patients with expected QoL difference. This analysis can classically be made reporting the mean difference in QoL score between groups with expected difference in QoL level. The known-group validity is reached if there is a statistically significance difference between the groups in all expected QoL dimensions. This analysis should thus be done on an appropriate sample size. The recommendation of the COSMIN initiative is to have at least 100 patients per group [17]. In case, significance is not reached in all dimensions expected, the results should be discussed between researches and experts associated to the validation process. As example, additional analyses could be explored in order to explain this unexpected result.

7.3.5 Criterion Validity

In case of assessment of the concurrent validity, the researcher confronts the QoL questionnaire to a "gold standard." In QoL field, this could be a very well-known QoL questionnaire for which the psychometric properties have been fully validated. It could be also a longer version of the current questionnaire. In that case, the comparison is generally made with a correlation analysis between the scores of the QoL instrument of interest and those of the "gold standard." To consider the concurrent validity to be reached, a correlation of at least 0.70 between both instruments

is expected [7]. In case of dichotomous "gold standard," the Area Under the Receiver Operator Curve (ROC) Curve (AUC) can be estimated [18]. An AUC of at least 0.70 is considered to be satisfying [7].

In case of predictive validity, the researcher will study the ability of the QoL instrument to predict future events or health status. For such kind of analysis, a longitudinal follow-up of the patients is thus required. If the researcher aims to study the association of QoL level with overall survival or disease progression, a Cox regression model could be performed. In this model, the baseline QoL score will be introduced as a covariate in the model. QoL score can be introduced either as continuous score or a dichotomization can be performed using the quartile as example. Predictive validity is reached if the QoL score is significantly associated with overall survival (or progression-free survival).

7.3.6 Internal Consistency

The most widely used method to assess internal consistency is the Cronbach's alpha coefficient [19]. This coefficient is also the most widely reported information of reliability in papers of validation of QoL questionnaires. This is due to the simplicity to compute this coefficient, often implemented in statistical software. It is also due to the single assessment needed, which is not the case for both reproducibility and measurement error. Considering a scale of n items, with x_i is response provided to the item i for all patients, the formula of Cronbach's α coefficient is:

$$\alpha = \frac{n}{n-1}\left(1 - \frac{\sum \mathrm{Var}\left(x_i\right)}{\mathrm{Var}\left(\sum x_i\right)}\right)$$

The α coefficient varies from 0 to 1. The most the items are consistent, the most the α coefficient increases. We generally consider that a α coefficient of at least 0.70 corresponds to a good internal consistency between the items [7]. However, the α coefficient increases with the number of items within the scale. A very high α coefficient could be the sign of redundancy between the items [20]. Some items could thus be deleted because they do not provide additional information. Conversely, if the α coefficient increases once deleting an item, it may suggest that this item has not a close internal consistency with other items of the scale. This item may assess another dimension of QoL. The α coefficient may thus be computed separately deleting one item at each time in order to detect this kind of problematic items. The α coefficient should be reported with its 95% confidence interval to allow a complete interpretation of the results and to have information about the precision of the results.

7.3.7 Test-Retest Reliability

For test-retest reliability estimation, patients should complete twice the QoL questionnaire. Patients selected for this analysis should be in stable disease. The choice of the time interval between the measurement occasions is thus crucial. It will depend of the population of interest. The objective is to find the best time interval. A too short interval could induce patients to remember the response provided at the first assessment (recall bias). Conversely, if the interval is too long, the patient may experience a change in his health condition which could impact his QoL assessment. In oncology, the time interval between the two assessments could vary between 2 weeks and 1 month in order to ensure the stable conditions of the patients. This analysis can be planned on patients in pre- or post-treatment to allow the requirement of a stable disease. While the design may guarantee to select patients in stable disease, researchers are encouraged to ask the patients to report any particular event which occurred between the two assessments. This is done to control patients who encountered an event which could impact the QoL assessment (e.g., an adverse event or death in the patient's relatives). Those patients would be excluded from the test-retest reliability analysis. The reliability is then assessed between the two measurement occasions. The use of a classic Pearson correlation to assess test-retest reliability is

tempting and sometimes used but should be advocated. In fact, due to the repeated measures on the same subjects, the correlation will be high by definition but not a sign of reproducibility of the measure.

The method used to estimate test-retest reliability will depend on the type of data analyzed. In case of dichotomous items, the Kappa coefficient of agreement is the recommended method to use:

$$\kappa = \frac{p_{\text{agreement}} - P_{\text{chance}}}{1 - P_{\text{chance}}}$$

Since patients could provide the same answer at both time points by chance, the proportion of agreement by chance (P_{chance}) is subtract to the total proportion of agreement ($p_{\text{agreement}}$). The Kappa coefficient varies between 0 and 1. A value lower than 0.2 represents a slight agreement, between 0.21 and 0.4 a fair agreement, between 0.41 and 0.6 a moderate agreement, between 0.61 and 0.8 a substantial agreement, and greater than 0.80 an almost perfect agreement [7]. For simple item with ordinal response scale, a weighted kappa can be used to estimate the test-retest reliability with the same interpretation as the kappa coefficient. For multi-item dimensions, the intra-class coefficient (ICC) is the recommended method. This method explores the proportion of the total variance that is associated with the inter-patient's variance. ICC can be obtained through ANOVA analysis. The ICC varies between 0 and 1. An ICC $\geq$ 0.70 is considered as satisfying [7]. To allow a complete interpretation of the results, the ICC should be reported with its 95% confidence interval.

7.3.8 Inter-rater Reliability

While most of QoL questionnaires in oncology are self-completed questionnaires, an indirect assessment has in some circumstances to be done. As example, an indirect assessment is sometimes required in pediatric or palliative care where it can be difficult for the patients to complete themselves the questionnaire. In case of an interviewed administration of the questionnaire or completion by a caregiver or healthcare provider, the inter-rater reliability has to be estimated. In that case, inter-rater reliability can be studied through ICC has for test-retest reliability. The same threshold of an ICC $\geq$ 0.70 can be used to consider the inter-rater reliability to be reached. Other possible analyses can be done such as regression analysis between the two raters.

7.3.9 Measurement Error

To allow measurement error estimation, researchers will need a longitudinal design among stable patients as for test-retest reliability estimation.

The Standard Error of Measurement (SEM), Smallest Detectable Change (SDC), or Limits of Agreement (LoA) are three possible indicators of measurement error for scores computed from QoL questionnaires.

The SEM equals to the square root of the error variance extracted from ANOVA analysis. Since this criterion is not easy to interpret, it can be used to estimate the individual SDC according to the following formula:

$$\text{SDC}_{\text{ind}} = 1.96 * \sqrt{2} * \text{SEM}$$

The SDC_{ind} is the smallest within patient change interpreted as the "real change" above the measurement error, and at the statistical level of 0.05 [21, 22].

The SDC at the group level ($\text{SDC}_{\text{group}}$) can also be obtained as follows for a sample size of n patients [22]:

$$\text{SDC}_{\text{group}} = \frac{\text{SDC}_{\text{ind}}}{\sqrt{n}}$$

The last possible representation of measurement error is through LoA which are graphically represented through Bland-Altman plot [23]. This graph represents the difference of the two paired measurements against the mean of the two measurements. The LoA boundaries have to be determined a priori and the following parameters are generally chosen:

$$\text{LoA} = \text{mean}_{\text{change}} \pm 1.96 * \text{SD}_{\text{change}}$$

Where:

- $\text{mean}_{\text{change}}$ is the mean change between the two measurement times
- $\text{SD}_{\text{change}}$ is the standard deviation of the change between the two measurement times

In this way, a change in scores within the LoA or smaller than SDC_{ind} can be attributed to measurement error. To consider the agreement as positive, the SDC or LoA should be lower than the minimal important difference if available (see Sect. 7.5) [7].

Researchers should report measurement error estimations in complement to test-retest reliability, which is not systematically done to date.

7.3.10 Responsiveness

The statistical analyses to determine the responsiveness of a QoL questionnaire will depend on the hypotheses formulated, the design, and the availability or not of a "gold standard." In any case, hypotheses should be formulated at the time of the design of the study and before to do any statistical analysis, In order not to introduce any bias in the results and interpretation.

If a "gold standard" is available, the analysis will depend on the type of data collected. In case of dichotomous QoL instrument (and of course, dichotomous "gold standard"), the percentage of sensitivity and specificity should be analyzed. The sensitivity is the percentage of patients with a positive QoL outcome according to the questionnaire of interest and with a truly positive QoL level according to the gold standard. The sensitivity is the percentage of patients with a negative QoL outcome according to the questionnaire of interest and with a truly negative QoL level according to the gold standard. The sensitivity and specificity should be as high as possible. For continuous scores, two types of analysis can be done. First, the correlation between the changes scores of both the QoL instrument of interest and the gold standard can be estimated. Second, the AUC can be estimated [18]. This AUC is done considering patients experiencing change between the two measurement times versus patients without change according to the gold standard. An AUC of at least 0.70 is considered to be satisfying [7].

In case of no available "gold standard," researchers can either plan to compare:

- Change observed within the QoL questionnaire of interest before and after an intervention.
- Changes observed between defined groups of patients among the questionnaire of interest.
- Change observed between the QoL questionnaire of interest and another instrument assessed at the same measurement times. In that case, the second questionnaire should highlight sufficient evidence of validation.

For change observed within the QoL questionnaire of interest before and after an intervention, different indicators can be reported to quantify the amount of change or assess the statistical significance of the results. The most widely used indicators are the Effect Size (ES) and the Standardized Response Mean (SRM). The ES equals to the mean change between the two measurements divided by the standard deviation of the baseline. The SRM equals to the mean change between the two measurements divided by the standard deviation of the change between the two measurements. For both indicators, a coefficient of 0.20 or less is considered as a small amount of change, between 0.21 and 0.50 as a moderate change and over than 0.50 as a large amount of change [24]. The SRM is more often reported in publications than the ES. Researchers generally recommend to report the SRM instead of the ES.

Changes observed between defined known-groups of patients among the questionnaire of interest can be analyzed using an analysis of variance or other adapted analysis for multiple groups.

Changes observed between the QoL questionnaire of interest and other instrument assessed at the same measurement times can be analyzed using different statistical models. These models can involve an analysis of variance or a regression model on the scores depending on the type

of data modelized. In each case, the choice of the model should be justified and adapted to the sample size.

A summary of main statistical analyses used to assess psychometric properties are presented in Table 7.1.

7.4 Required Sample Size to Validate a QoL Scale

To ensure that the psychometric properties have been assessed with an enough precision, a validation study of a scale must be conducted with an appropriate sample size. As for any quantitative study, we thus need to determine the sample size required to conduct the validation of a newly developed QoL questionnaire. However, a recent literature review highlighted that few studies justified the number of patients included to validate a patient-reported outcome questionnaire [25]. This review was not limited to cancer domain neither to QoL questionnaires, but it can suggest that an effort is still needed to improve the quality of QoL questionnaire validation studies.

The sample size required will depend on multiple parameters: the psychometric properties that we would like to assess, the statistical methods that will be used, the number of items that the scale contains, and the number of a priori QoL dimensions assessed. The sample size must also take into account the proportion of missing data expected.

The COSMIN initiative group proposed minimum sample size requirement to consider the study as high quality [17]. These rules and thresholds are very helpful and simple for the researchers to follow while designing their validation study. As example, the number of minimum sample size requirement for content validity is equal to 7 for qualitative studies and to 50 for quantitative studies. For factor analyses to assess the structure of the questionnaire, at least 7 patients per item and a minimum of 100 patients have to be included. For Rasch family models, at least 200 patients are required. For Cronbach's alpha analysis, at least 100 patients are required. However, these minimum sample size requirements are not sufficient. A sample size estimation taking into account characteristics of the questionnaire and the parameters of the models applied is still needed. This estimation can most of the time be made on a dedicated sample size estimation software. A sample size can be estimated through confidence interval of the estimation. For example, using PASS (Power analysis & sample size) software, we obtained the following sample size for:

- Correlation Analysis:

When the estimate of Pearson's product-moment correlation is 0.300, a sample size of 320 produces a two-sided 95% confidence interval with a width equal to 0.200 [26].

- Cronbach's Alpha:

Considering a dimension of 5 items, a sample of 348 subjects produces a two-sided 95% confidence interval with a width of 0.100 when the estimated coefficient alpha is 0.700 [27].

Considering a dimension of 10 items, a sample of 309 subjects produces a two-sided 95% confidence interval with a width of 0.100 when the estimated coefficient alpha is 0.700.

- ICC:

Considering an ICC of 0.70 as interesting, with a two-sided 95% confidence interval with a width of 0.100, a random sample of 403 subjects is required with two assessment times [28].

7.5 Interpretability

The interpretability is also a crucial characteristic of a QoL questionnaire to interpret the results. However, it does not strictly belong to the psychometric properties of a questionnaire. Since a confusion can exist in the terms involved in interpretability, this characteristic is presented separately in order to give some elements of interpretability. Indeed, the interpretability can

Table 7.1 Main statistical analyses and specific requirement for each psychometric property [17]. (Based on COSMIN)

Measurement property	Statistical analysis	Specific model	Specific conditions of use	Threshold to consider good measurement property or goodness of fit
Construct validity				
Structural validity	Exploratory factor analysis	Varimax rotation (no correlation between dimensions)	No hypothesis on the underlying structure	
		Oblimin rotation (correlation between dimensions)		
	Confirmatory factor analysis		Hypotheses on the scale structure	RMSEA <0.06
				CFI >0.95
				Chi-square >0.05
	Item response theory	Rasch model	Dichotomous item	RMSEA <0.06
				CFI >0.95
				Chi-square >0.05–2.5 < item fit <2.5
		Partial Credit Model	Ordinal response scale	RMSEA <0.06
				CFI >0.95
				Chi-square >0.05–2.5 < item fit <2.5
Convergent validity	Multitrait multimethod analysis			Correlation >0.30 with a priori related dimension
Divergent validity	Multitrait multimethod analysis			Correlation <0.30 with a priori unrelated dimension
Known-group validity	Mean difference in QoL scores		Continuous scores	*P*-value <0.05
Criterion validity				
Concurrent validity	Correlation analysis		Continuous scores	Correlation ≥0.70
	Area Under the ROC Curve (AUC)		Gold standard with dichotomous values	AUC ≥0.70
Predictive validity	Cox regression model		Time to event data	*P*-value <0.05
Reliability				
Internal consistency	Cronbach's α coefficient		Multi-item scales	α >0.70
			Ordinal responses	
Test-retest reliability	Intra-class coefficient (ICC)		Repeated measures on same subjects	ICC >0.70
			Continuous scores	
	Weighted kappa		Repeated measures on same subjects ordinal scale	Weighted kappa >0.70
Measurement error	Smallest Detectable Change (SDC)		Continuous scores	SDC <minimal important difference
	Limit of Agreement (LoA)		Continuous scores	LoA <minimal important difference

(continued)

Table 7.1 (continued)

Measurement property	Statistical analysis	Specific model	Specific conditions of use	Threshold to consider good measurement property or goodness of fit
Responsiveness	Effect sSize (ES)		Continuous scores	ES >0.20 for moderate amount of change
	Standardized Response Mean (SRM)		Continuous scores	SRM >0.20 for moderate amount of change

be determined at the time of the validation of the questionnaire.

The interpretability has been defined as the degree to which one can assign qualitative meaning that is, clinical or commonly understood connotations to an instrument's quantitative scores or change in scores [1]. Different indicators can thus be useful to allow the interpretation of QoL questionnaires. The COSMIN and other independent researchers recommend to report at least the following information:

- The norm values for reference population, using the mean and standard deviation indicators at least. It could be useful also to report this information for specific subgroups of patients, for example, according to disease stage, age, gender, and the treatment phase (i.e., before and after treatment).
- The percentage of missing items and missing scores for the population studied.
- The percentage of floor and ceiling effects.
- The minimal important difference (MID).

The MID has been defined by Jaesckhe et al. as "smallest difference in score in the domain of interest which patients perceive as beneficial and which would mandate" [29]. The MID must be determined for each questionnaire and can be specific to the score, the population, and the direction of change for longitudinal data (i.e., improvement or deterioration). Moreover, this threshold can be determined for both individual-level change (e.g., responder threshold) and group-level change. The MID is useful to interpret the results of HRQoL data in terms of clinical relevance. It is also key information to determine a sample size estimation for any study using QoL as the primary endpoint.

Different methods exist to estimate the MID and responder threshold. They are generally separated into two categories, namely, anchor-based methods and distribution-based methods. Anchor-based methods used an external criterion to characterize the patients' change profile of QoL level. This "anchor" will allow to split the patients in different categories: patients presenting a priori a stable QoL level, a low improvement/deterioration of QoL, or a high improvement/deterioration of QoL. The anchor should have a clinical meaning. It could be the toxicity grading, the disease progression, or patients' subjective judgment of QoL change. Recommendations are to use multiple anchors to compare the results. Anchor-based methods can be used either to estimate MID at the group-level change and the responder threshold for individual-level change. At the group-level change, one easy method to characterize the MID is to report the mean change between two measurement times for patients experiencing a low QoL improvement/deterioration according to the anchor. At the individual-level change, the responder threshold could be obtained with the AUC under the ROC curve. Analysis will be done comparing patients experiencing low improvement versus no change on the one hand, and patients experiencing low deterioration versus no change on the other hand. Distribution-based methods are used for group-level MID. They used the score distribution to characterize the MID. For example, a percentage of the standard deviation can be considered as the MID. The percentage the most widely used is 50% of the standard deviation of the score. Any change above this threshold will be considered as clinically significant. One advantage of the distribution-based method is its simplicity. It does not need an external criterion to characterize the patients' change. However, the MID obtained are the same for both improvement and deterioration, while MID is often larger for improvement than for deterioration.

The current recommendation is to combine both anchor- and distribution-based methods to estimate the MID [30]. As for all statistical analysis, the MID should be determined with an appropriate sample size. However, most of studies published on MID used available data either from randomized clinical trials or observational cohort. Moreover, due to the complexity of MID determination, we recommend to pursue the researches on MID even for questionnaires with existing MID thresholds. A meta-analysis could then be done like it was already explored for EORTC QLQ-C30 questionnaire [31, 32].

7.6 Conclusion

The validation of the psychometric properties of a QoL questionnaire is a very long process that should be done rigorously in order to be confident on the QoL results. Researchers should be aware of the difficulty of the process in which they are engaging before to develop a new QoL questionnaire. Due to this complexity, it is important to justify the necessity to develop and validate a new QoL questionnaire. This chapter could then be a support for researchers in order not to forget any important property to validate. It provides also recommendations for main statistical methods to apply with an appropriate sample size. We encourage researchers to follow the COSMIN checklist for designing a validation study to ensure a high-quality validation study. Finally, one validation study is often not enough to collect sufficient information on the psychometric properties of a questionnaire. It is important to continue to explore the validity of available questionnaires through additional researchers.

7.7 Questions That Can Be Used for Learning/Testing

- Once developing a QoL questionnaire, we need to find a balance between exhaustiveness and redundancy. What could be the consequence of redundant items? In contrast, what could be the consequence of missing important information for the target construct?
- When determining the structure of the scale, the objective is to separate the items per dimension. Thus, one item should assess a single QoL domain. What could be the consequence of the overlap of items between several dimensions?
- The Cronbach's alpha coefficient was calculated on an entire questionnaire which contains 50 questions. A value of 0.90 was obtained and the researcher concludes that the internal consistency is very high. The researcher also concludes that a unidimensional model can be retained with the estimation of the single summary score. Is this a good interpretation?
- A QoL questionnaire was originally developed in an English-speaking country. A four-factor structure was retained according to a CFA. The use of the CFA was justified by the researchers according to the a priori domains explored. This scale was then adapted in Spanish. Researchers used an EFA to explore the scale structure and found a five factors structure. Indeed, the fifth factor is not the result of a split of one factor of the original English version. What could be the consequence for the use of the questionnaire in an international study involving both English and Spanish countries?

7.8 A Topic for Discussion That Can Be Used in Teaching

Validation of the psychometric properties of a QoL questionnaire is an important and long process. Different psychometric properties need to be studied which requires data collected in a longitudinal design. In general, at least 5 years of research are needed between the proposal of questionnaire development and the final validated questionnaire. This very long process does not match with the dynamic of treatments research in many cancer sites. In fact, questionnaires developed to assess symptoms for patients receiving chemotherapy or radiotherapy and their impact on patients' QoL are probability not adapt to patients receiving new treatment strategies, including targeted therapy and immunotherapy. Therefore, researchers should

rethink and probably adapt the process of questionnaire development and validation. Computer Adaptive Testing (CAT) was recently developed in oncology in order to optimize the QoL assessment. Using a CAT, patients will complete items from an item bank. Each patient will complete a selection of the items, chosen according to the responses provided to previous items. The selection is thus adapted to the patient, reflecting the individual QoL's assessment. As for classical "static" questionnaires, the psychometric properties of the CAT need to be assessed. However, this personalized process of QoL assessment could be more adapted to the area of precision medicine.

7.9 Further Reading List

This chapter presents a summary of psychometric properties and statistical considerations for QoL questionnaire validation. However, we invite interested readers who need more details to read the following books:

- For complements on scale development: Streiner DL, Norman GR, Cairney J. Health measurement scales: a practical guide to their development and use. Oxford University Press; 2015.
- For more details on measurement properties and statistical methods for QoL questionnaire: Fayers PM, Machin D. Quality of life: the assessment, analysis and reporting of patient-reported outcomes. Wiley; 2015.
- For more details on IRT models: de Ayala RJ. The theory and practice of item response theory. Guilford Press; 2013.

7.10 Research in Context

The Expanded Prostate Cancer Index Composite (EPIC) questionnaire was initially developed in English language to assess QoL and symptoms of patients with prostate cancer [33]. In order to use it in non-English-speaking countries, it is necessary to adapt it to the language of interest and to validate the psychometric properties of the new questionnaire. Here, a brief summary of the French validation of the EPIC questionnaire is presented [34].

This questionnaire contains 50 items allowing to assess 4 domains of QoL according to the original English validation, namely, the urinary, bowel, sexual, and hormonal domains. Each domain is separated into function and bother subscales.

For this French validation, 215 patients were included: 90 in a cured group to assess test-retest reliability and 125 in a treatment group to assess responsiveness. Patients completed twice the questionnaire: at inclusion (T1) and 2 weeks later (T2) for cured group; at inclusion (T1), corresponding to the diagnosis and before the initiation of treatment, and at the end of the treatment (T2) for the treatment group.

The structural validity was assessed using exploratory factor analysis. The same structure and decomposition as for the original version were obtained. Both internal consistency and test-retest reliability components of the reliability domain were explored. Analyses were done for each domain and subscale. Internal consistency was explored using Cronbach's alpha coefficient at T1. Test-retest reliability was explored using both assessment times among patients of the cured group with ICC. A description of QoL scores for the four domains at baseline as well as percentage of floor and ceiling effects as elements of interpretability are reported along with statistics of reliability (Table 7.2). Clearly, the Cronbach's alpha is over 0.70 for all domains except the sexual domain (α = 0.61). No confidence interval is reported to estimate the precision of the estimation. The ICC was also over the threshold of 0.70 for all domains reflecting a good test-retest reliability. Unfortunately, the measurement error was not reported to

Table 7.2 Baseline QoL level per domain of patients included in the French EPIC validation and reliability assessment

	Number of items	*N*	Mean (SD)	Floor effect (%)	Ceiling effect (%)	Cronbach's α	ICC
Urinary	12	167	86.74 (13.61)	0	9.30	0.88	0.90
Bowel	14	165	91.70 (9.93)	0	15.35	0.61	0.86
Sexual	13	177	43.88 (21.98)	0.93	0	0.89	0.94
Hormonal	11	162	87.67 (12.49)	0	20.93	0.77	0.89

Adapted from Anota et al. [34], Tables 2 and 3. Some modifications were made. https://doi.org/10.1186/s12955-016-0571-y, licensed under the terms of the Creative Commons Attribution 4.0 International License (http://creativecommons.org/licenses/by/4.0/)

complement these results on the reliability quality domain. The authors conclude that the French version is validated with similar properties as for the original English version. Due to the low Cronbach's alpha for the sexual domain, future researches could be done to confirm and complement the results obtained. The assessment of both measurement error and minimal important difference is of particular importance.

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Using New Technologies in Quality of Life Assessment

8

Kedar K. V. Mate

Contents

8.1 Introduction

The word 'patient' originates from Latin word 'patiens'. Google search of origins of the word 'patient' is accompanied by adjectives such as long-suffering, tolerant, unyielding, experiencing, stubborn, endured, among others, words that are offensive, derogatory, and inaccurate reflection of a person who seeks care. Over time, the word 'patient' is falling out of context, and the use of people-first language is encouraged in clinical practice and research, for example, people living with HIV, person post-stroke, etc. People-first language is positive, dignified, humanizing, and respectful to the individual. The first usage for people-first language was by Beatrice Wright in her book Physical Disability: A Psychological Approach [1]. Over time the people-first language entered into healthcare practice and research. The biggest boost to the

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A. Kassianos (ed.), *Handbook of Quality of Life in Cancer*,
https://doi.org/10.1007/978-3-030-84702-9_8

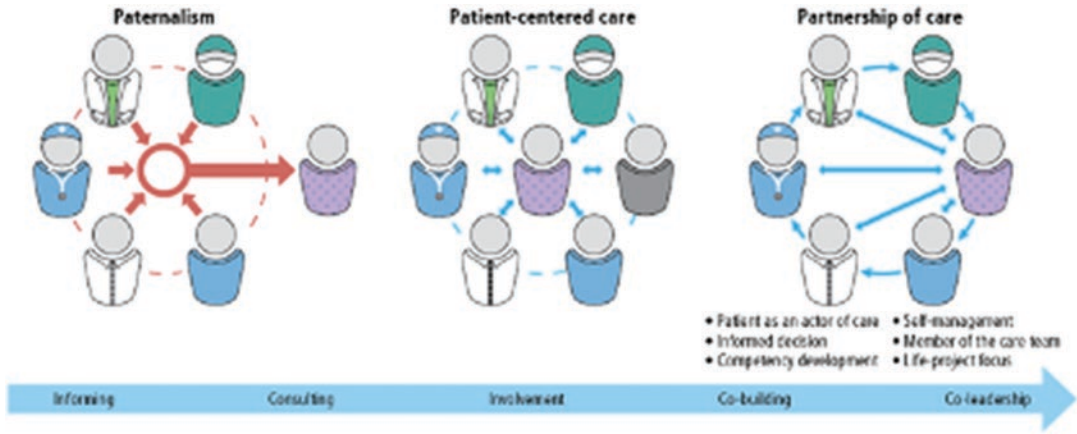

Fig. 8.1 The patients' care models (Adapted from Comité sur les pratiques collaboratives et la formation interprofessionnelle, 2013 [25]). Used with permission from Longwoods Publishing Corporation [26]

use of people-first language was following Denver Principles in 1983 that used 'People With AIDS' [2]. Other terms that are frequently used are 'client', 'user', 'healthcare receiver (in contrast to healthcare providers)', 'health seeker', 'consumer', and in research 'subject' or 'participant'. The term 'patient' is now considered an umbrella term inclusive of individuals with personal experience of a health issue and informal caregivers, including family and friends. The term is extended to include members of key groups or communities affected by a given health issue [3]. For the purpose of this chapter, we will use the term patient to reflect a collective group of individuals who use healthcare services.

The transformation of healthcare models has conceptualized by Karazivan and colleagues (Fig. 8.1). The paternalist approach has minimal patient involvement and is centered around the healthcare provider. The patient-centered approach moves the patient from the periphery to the central and now is the main focus of the care plan. The modern approach to treatment is the patient-as-partner approach, where the patient is part of the healthcare team and decision-making process [4, 5].

The role of patient and patient as a source of information has become critical in modern medicine. The role of the patient has moved from 'something that is done to it' to 'something done for it, by it'. The transformation of this approach has become vital in almost all fields of clinical practice and research. It would be almost impossible and possibly unethical to develop a tool, test an outcome measure, or treatment without the direct involvement of patients and their caregivers in the process. The national health agencies such as the Food and Drug Administration [6] and the European Medicines Agency [7] have been transformative in helping a patient become a central member of the healthcare system [6, 8, 9].

This chapter will enable readers to be familiar with (a) sources of data; (b) health outcomes; (c) technologies for telehealth; and (d) social media as a technology.

8.2 Sources of Data

Where does the data come from? The data in health statistics come from the patient, or interaction of the patient with other people, or utilization of resources such as healthcare services. Patient data are typically collected for two main purposes: clinical decision-making and research. For either purposes, data is either collected directly from the 'body', for example, vital signs and imaging, or asked the person to reflect and report on their health or their experience, for example, symptoms, mental health, access to hospital building, or an attitude of the healthcare provider. Till now data is primarily collected for purposes to make a clinical decision or answer a research question often leaving patients out of the process to make these decisions. However, there

is a slow but definite movement toward making patient's own data accessible to them and engage them in participatory data analysis [10]. From the patient's perspective, data on health is not only for identifying trends suggestive of change in health status or function but also for comparing their health over time, monitoring, and perhaps establishing goals to improve behavior. Not all data collected is for the purpose of decision-making or initiating treatment. Several online and mobile applications are created to make a patient's own data accessible and interpretable and engage different data visualization technologies. For example, Hsieh and colleagues developed LifeStreams, a modular sense-making toolset to identify important patterns from everyday life using integrated analysis [7].

8.3 Health Outcomes

Quality of life (QOL) is a multidimensional construct and has many dimensions (or facets) such as material comforts, safety, relationship, learning, creative expression, participation in social and public affairs, leisure, help others, and more. The health-related quality of life (HRQL) is embedded in QOL. The literature suggests QOL to be a subjective construct that evolves over a period and is different across people and geographical regions. One could consider QOL as a valuation or perception of the difference between what one can actually do and what one wishes to do. HRQL are those aspects that are within the purview of the healthcare system to treat, manage, or support. HRQL typically covers physical, functional, emotional, and social well-being.

Patient-reported outcome [8] is a measurement of any aspect of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else [8, 11, 12]. PRO captures symptoms such as pain severity, fatigue, and nausea, functional status such as physical function like walking difficult or psychology function such as mood, satisfaction with treatment, or adherence to medications. In other words, constructs that measure 'difficulty' are captured using PRO as only the person themselves can say how difficult an activity is. In addition to collecting information on patient'e health status, data can also capture information about patients' interaction with the care services and their experiences with healthcare professionals. These type of data reflects patient's experiences, satisfaction, perspectives, needs, and priorities. PROs that capture patients' experience with healthcare services and delivery are called patient-reported experience measures [13] which will be discussed later in the chapter.

A PRO can be captured by self-report or by interview, provided that the interviewer records only the patient's response and does not interpret responses. Clinically reported outcomes or ClinROs are reports coming from a trained healthcare professional regarding their interpretation of signs or behaviors that can be observed related to a patient's disease or condition, for example, the expanded Disability Status Scale. The observer-reported outcomes or ObsROs are assessments of observable signs, events, or behaviors related to a patient's health condition as reported by individuals who observe the patient in daily life, like parents or caregivers. Performance outcomes or PerfOs are measurements collected when a patient is asked to complete a well-defined, repeatable, and standardized task such as a 6-min walk test. Mayo et al. have linked different sources of information as shown in Fig. 8.2 [14].

Table 8.1 shows the different constructs and the optimal source of information that is captured. PRO data is collected for two main purposes: research and clinical care. PRO data collected to guide clinical care have several advantages such as improve the quality of care, reduce healthcare expenditure, early detection of change in patient health status or well-being, guide treatment-related decision–making, and improve overall quality of life and patient satisfaction [15, 16]. In spite of several advantages, routine data collection for PROs is challenge due to technological and logistical limitations. Apart from the fact the PRO measures used to collect data during routine clinical visits should be psychometrically robust, actionable, and interpretable, the methods to collect data should be done with user-friendly technologies, be short and time-efficient, and be cost-effective and other systemic issues such as lack of time, personnel, and infrastructure. PRO data collected for research purposes is detailed but tends to be a very costly affair.

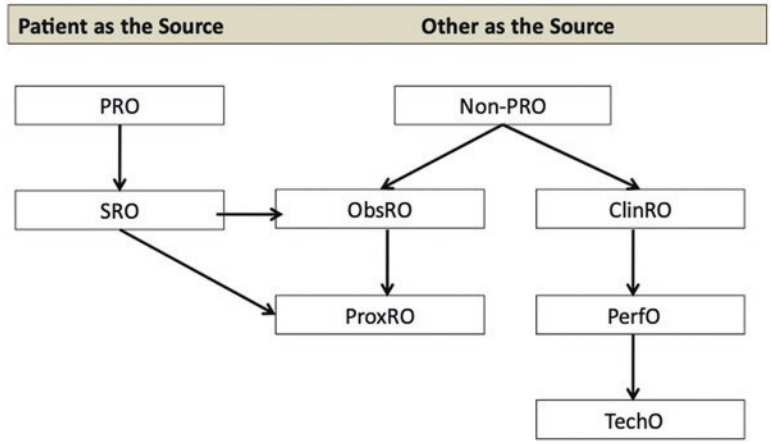

Fig. 8.2 Suggested linkages between sources of outcome information [14]. ClinRO, Clinician-reported outcome; ObsRO, observer-reported outcome; PerfO, performance-reported outcome; PRO, patient-reported outcome; ProxRO, proxy-reported outcome; SRO, self-report outcome; TechO, technology-reported outcome. (Reprinted from *Journal of Clinical Epidemiology*, Vol. 89, Nancy E. Mayo, Sabrina Figueiredo, Sara Ahmed, & Susan J. Bartlett, Montreal Accord on Patient-Reported Outcomes (PROs) use series – Paper 2: terminology proposed to measure what matters in health, p. 119–124, Copyright 2017, with permission from Elsevier)

Table 8.1 Taxonomy and concepts of health outcomes assessed according to source of information [14]. (Reprinted from *Journal of Clinical Epidemiology*, Vol. 89, Nancy E. Mayo, Sabrina Figueiredo, Sara Ahmed, & Susan J. Bartlett, Montreal Accord on Patient-Reported Outcomes (PROs) use series – Paper 2: terminology proposed to measure what matters in health, p. 119–124, Copyright 2017, with permission from Elsevier)

Outcome	Patient-reported outcome (PRO)	Non-PRO		
		Self-reported outcome (SRO)	Observer/proxy-reported outcome (ObsRO/ProxRO)	Clinician/performance/technology-reported outcome (ClinRO/PerfO/TechO)
Biological parameters				Laboratory test or image (TechO)
Symptoms	Intensity, impact, bother	Frequency, duration	Frequency, duration	
Physical impairments		Physical appearance, mobility, movements	Physical appearance, mobility, movements	Physical examination (ClinRO); performance (PerfO)
Cognitive impairments		Type, frequency, impact, change	Behavior	Performance (PerfO)
Function: activity, participation	Difficulty, satisfaction	Limitation, restriction	Limitation, restriction	Performance (PerfO)
Health	Perception			Health status (ClinRO. PerfO; TechO)
Quality of life	Perception			

Clinical outcome assessments (COAs) are a mix of PROs, ClinROs, ObsROs, and PerfOs and form primary or secondary endpoints in a therapeutic clinical trial as required by the US Food and Drug Administration (US-FDA) [17]. Collecting PRO information has moved from traditional approach based on paper-and-pencil to using technologies such as electronic PROs (ePROs). Several studies have highlighted challenges with paper-and-pencil method of data collections, mainly unreadable, missing, illogical, or faulty useable data [18]. ePROs system of data collection could be expensive at first due to cost incurred for trained personnel, devices, software, and data storage, but in long term, ePRO is cost-effective. Studies have shown that data collected using electronic platforms tends

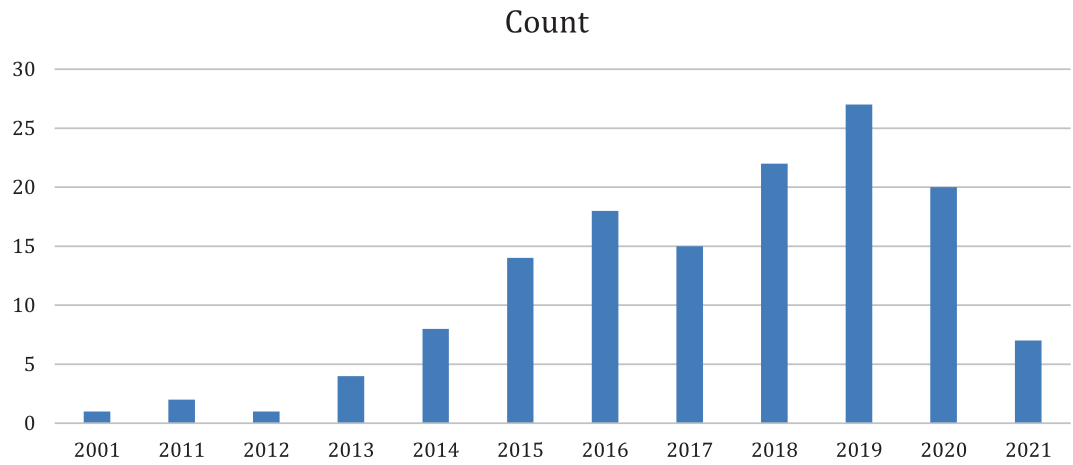

Fig. 8.3 Trend in number of articles published on PubMed that used 'Yelp' social media as a source of information

to complete, with little to no errors, less administrative challenges, increased patient engagement, and therefore higher completion rates [19].

Computerized uses of PROs assessment address many of the challenges encountered during routine clinical data collection. Computerized adaptive testing (CAT) uses PRO based on item response theory (see also Chap. 9, this volume). Technologies to capture PRO data include interactive voice response [20], laptop, computers, tablets with touch-screen features, online platforms such as REDCap, DATSTAT, HealthMeasures, Epic, CODE Technology, and several other Web-based surveys. Tablets and smart phones are the most frequently used devices to collect PRO data because of the ease to carry and reach to people with limited strength or mobility.

For people seeking services, survival and return to optimal function alone are not sufficient. The health outcomes are directly impacted by the service patients and their family members receive. The experience of the patients and their families with healthcare services and delivery is also important. This includes interactions with healthcare providers such as doctors, nurses, pharmacists, or other staff. The feedback from the patients helps identify gaps in the care. The aspect of patient experience has been increasingly reported in research but also regularly assessed as a part of quality assurance and monitor performance. The concept of patient experience and satisfaction are used interchangeably but are not the same. The term patient satisfaction is the extent to which patient's expectations are met and therefore an individual-level parameter. Two people receiving exactly the same service may still have a vastly different expectations and therefore satisfaction.

Some countries and government collect information on patient experience through national survey. AHRQ's Consumer Assessment of Healthcare Providers and Systems (CAHPS) is one such tool that is widely used by the organizations to assess the patient-centeredness of the care. The CAHPS Cancer survey is implemented in outpatient and inpatient settings such as community oncology practices, cancer centers at community hospitals and at tertiary care teaching hospitals. The survey covers radiation and medical oncology and cancer surgery.

Patient experience of healthcare services and interaction with healthcare providers and staff could be collected from social media website. This data could be collected to capture information on patient interaction with the healthcare system and personnel. A PubMed search for popular social media website Yelp in April 2021 showed increase in number of articles that use data from social media to study experiences (Fig. 8.3).

8.4 Technologies for Telehealth

The Health Resources and Services Administration (HRSA) of the US Department of Health and Human Services defines telehealth as the use of electronic information and telecommunications technologies to support and promote long-distance clinical health care, patient and professional health-related education, public health, and health administration.

Technologies include videoconferencing, the internet, store-and-forward imaging, streaming media, and terrestrial and wireless communications. In the era of COVID-19 pandemic, there has been a rapid surge in different technologies to support, monitor, track, and connect with patients. Use of internet-based technologies for delivery of health services through an online environment requires patient focus, participation, and empowerment to take charge of one's health [21]. The telehealth applications are grouped into four major classes of technologies.

- Live (synchronous). There are several different definitions proposed, three of the most frequent ones are the one by US Department of Veterans Affairs [6] which states synchronous telemedicine requires the presence of both parties at the same time and a communication link between them that allows a real-time interaction to take place. The second one proposed by the American Telemedicine Association (ATA) according to which synchronous telemedicine is interactive video connections that transmit information in both directions during the same time period, and third by the University of Miami (UM) Miller School of Medicine definition that real-time telehealth sessions are live and interactive and frequently use video-conferencing technologies. Often, special telehealth-enabled instruments, such as a video otoscope or an electronic stethoscope, are operated by a nurse or technician at the consulting provider's direction to remotely perform a physical examination. The underlying features of synchronous include a two-way real-time communication between the patient and the care provider, for example, videoconferencing.
- Store-and-forward (asynchronous) is defined by the Office of the National Coordinator for Health Information Technology where there is transfer of patient-related information such as history to a health practitioner. In this mode of communication, the data transfer does not occur simultaneously.
- Remote patient monitoring (RPM): the use of connected electronic tools to record personal health and medical data in one location for review by a provider in another location, usually at a different time.
- vMobile health (mHealth) where mass distribution of health care and public health information is passed through electronic interfaces such as mobile devices. The information could include general educational information, targeted texts, and notifications about disease outbreaks.

8.5 Social Media as a Technology

Traditional recruitment strategies involve print media such as flyers, newspaper advertisements, posters in hospitals and clinics, pamphlets, mass media such as television or radio announcements, etc. These strategies of patient recruitment have a relatively modest success in meeting the recruitment targets. Both the print and mass media as recruitment strategies are expensive and the print media specifically could have limited reach with respect to the geographical areas. Use of social media as an additional source to traditional methods of patient recruitment for clinical research is relatively new. The two methods of recruitment, social media review (SMR) and social media listening (SML), are the most popular way to recruit participants. There are several advantages to using social media for recruitment. The use of social media reduces recruitment times and screening failure rates and increases meeting recruitment targets and is a cost-saving approach in an already expensive clinical research [22]. The use of social media as a recruitment strategy is especially successful when conducting research in rare health conditions as social media can help disseminate information and reach necessary numbers that would not be possible using traditional approaches.

The US Centers for Disease Control and Prevention (CDC) describes social media as "tools to disseminate health messages" and "expand reach, foster engagement and increase access" to health messages [23]. Social media platform includes social networks such as Facebook, Blogs, Microblogging like Twitter, and media creation platforms such as Wikipedia, YouTube, Podcasts, etc. Several classifications are reported in the literature, for example, general purpose online social networks such as Facebook, Twitter, and virtual health communities such as Inspire (https://www.inspire.com) or ask-a-doctor (http://mdtalks.com/) [24]. Each has

advantages and disadvantages such as accessibility, participations, richness, and others. Social media has also been used to capture information on experiences with the healthcare providers and health services delivery. This information is used by people to select their site or physician for care. Increasingly, people are writing about their experiences online and this rich source of information tapped into as a quality measure of the institutions.

8.6 Conclusion

There is a need to acknowledge the increasing central role of patient in clinical care and research. All stakeholders involved in healthcare pathways and research teams should involve patient in the process early-on. Increasingly, various technologies and online platforms are available to collect patient-reported outcomes. Within the context of ongoing pandemic, various new and existing online platforms are renewed to deliver healthcare services to patients, and social media is gaining popularity as a source of patient information. How these sources guide future healthcare decisions remains to be seen.

8.7 Questions That Can Be Used for Learning/Testing

- What are PROs? Difference between PROs and PROMs?
- What are different sources of information and how they complement each other?
- What are the most common ways to collect PROs information and can you state a few advantages and disadvantages?

8.8 A Topic for Discussion That Can Be Used in Teaching

- Can you reflect back on the time when you received any healthcare service, and share your experience on how you were addressed by the hospital staff/nurses/physician/receptionist, etc.? What do you think of that encounter? Is there something you would have liked to hear or done differently?
- What are challenges in collecting PROs using technologies?
- Can you think of any factors, patient or technology that could affect how PROs data is collected?
- How would be introduce a person to PROs?
- What are ethical/privacy issues when using social media as a source of information?

8.9 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

1. Guidance for Industry Patient-Reported Outcome Measures: Use in Medical Product Development to Support Labeling Claims.
2. Measurement in Medicine: A Practice Guide: Henrica C. W. de Vet, Caroline B. Terwee, Lidwine B. Mokkink, Dirk L. Knol VU University Medical Center, Amsterdam.
3. Developing a Valid Patient-Reported Outcome Measure: NE Rothrock, KA Kaiser, and D Cella.
4. Patient-Reported Outcomes (Pros) and Patient-Reported Outcome Measures (Proms): Theresa Weldring and Sheree M.S. Smith.
5. The COSMIN checklist for evaluating the methodological quality of studies on measurement properties: A clarification of its content Lidwine B Mokkink, Caroline B Terwee, Dirk L Knol, Paul W Stratford, Jordi Alonso, Donald L Patrick, Lex M Bouter & Henrica CW de Vet.

8.10 Research in Context

Health-related quality of life is now an important outcome in drug trials and development of new intervention or therapies. There has been tremendous amount of work done in the last decade or so in developing new and testing existing patient-reported outcomes (PROs) instruments. This is following the publication of a guidance report for industry by the US Food and Drug Administration on use of patient-reported outcome measures (PROMs) in medical product development to support labeling claims (draft was published in 2006 and final in 2009) [6]. The report highlighted the need for incorporating patient's voice in the development of the PRO instruments as opposed some of the historical questionnaires constructed by clinician consensus alone. The pharmaceuticals are now required to demonstrate that new products go beyond decreasing disease-defying symptoms and show benefit on PRO instruments. The guidance report also provided steps to develop PRO instruments, demonstrate psychometric properties, include PROs as endpoints, and data analysis of the instruments in clinical trials. The method proposed in the report is still used today in developing PROs tools. Following this report, there were discussions and debates in the pharmaceutical and health outcomes research community and a big toward meeting the rigorous standards set by the report in testing and development of PROs instruments. Though there has been an overall positive change in health outcomes research world, there are some reports on limited update and suboptimal implementation of the PROs.

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9 Modern Psychometric Measurement and Computerized Adaptive Testing

Conrad J. Harrison
and Christopher J. Sidey-Gibbons

Contents

9.1 Introduction

There are many different domains of health that are affected by cancer and its treatment [1]. Some of those constructs, for example, psychosocial well-being, fatigue, and depression, cannot be quantified by standard medical investigations. These are referred to as latent constructs and are typically measured using validated questionnaires known as patient-reported outcome measures (PROMs). A typical PROM contains a series of items (questions), usually between 10 and 30, to which a patient must respond. The responses to the items are summed to produce a

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score indicating the level of the latent construct that the patient has.

There has been increasing interest in the use of PROMs as tools to measure outcomes that are important to patients in clinical practice and research. In clinical practice, PROMs can be used to assess and monitor symptoms and identify early clinical deterioration. When used to monitor disease progression in patients with metastatic solid organ tumors, for example, remote symptom monitoring with PROMs is associated with decreased symptom burden, fewer acute hospital attendances, and improved survival [2, 3]. Patient-reported outcome measures are frequently used as primary outcome measures in clinical trials and to support pharmaceutical licensing and clinical commissioning [4].

There are a vast number of latent constructs that can be measured using PROMs, and patients are often asked to complete multiple questionnaires at individual time points. This has led to concerns about increasing patient burden by asking too many items. Response burden can negatively affect the quality of PROM data, for example, when response fatigue reduces a participant's motivation and concentration or overall response rate. This might be particularly important in cancer, where disease and symptom severity could directly relate to a respondent's ability to complete burdensome questionnaires. In this case, significant bias can result from missing data [5].

Because PROMs are carefully designed to produce accurate measurements, it is typically not possible to just omit items from the questionnaire in order to reduce burden. This could impact the accuracy and reliability of results. However, there are techniques which can be used to reduce the length of questionnaires while maintaining the accuracy of the scores they produce. One such technique is known as computerized adaptive testing (CAT). Computerized adaptive testing refers to a process by which a computer algorithm iteratively selects only the most relevant and informative items for the patient to respond to, based on the responses they have already provided [6].

It is possible to apply CAT to any questionnaire that has been built or validated with modern psychometric theory. This can substantially reduce the length of questionnaires without affecting the validity of the scores that they produce. In this chapter, we will introduce the principles of modern psychometrics and CAT and describe how these are being applied to measure latent constructs in cancer.

This chapter will enable readers to: (a) understand the advantages of modern test theory over classical test theory; (b) understand the principles of computerized adaptive testing; and (c) describe examples of computerized adaptive tests used to measure quality of life in cancer.

9.2 Modern Test Theory

Psychometrics can be divided into two paradigms: classical test theory and modern test theory. Classical test theory was developed at the turn of the twentieth century by researchers including Charles Spearman and Lee Cronbach and relies on correlational statistics to provide evidence of questionnaire validity and reliability [7]. These analyses are versatile and straightforward to conduct and understand, but they only indicate psychometric performance at the level of the whole questionnaire (and not the individual items).

Modern test theory has two major advantages to classical test theory. First, modern test theory provides interval-level measurement (as opposed to ordinal measurement) [8, 9]. This means that latent constructs can be measured across a continuum with equidistant graduations (i.e., the difference between a score of 45 and 50 is exactly equal to the difference between a score of 50 and 55). This is not the case in ordinal, classical test theory PROMs. Second, modern test theory measures latent constructs probabilistically, at the item level. This means individual scores can be presented within a confidence interval (based on their standard error of measurement), and two respondents' scores can be compared even where they have answered different items from the same questionnaire [6]. This principle is fundamental to CAT.

9.3 Assumptions of Psychometric Models

Most modern test theory models assume that the chance of endorsing a particular item response relates only to the level of a single measured latent construct and the properties (parameters) of that item.

One key aspect of this assumption is unidimensionality. Questionnaires are described as unidimensional if each item measures the same latent construct and multidimensional where different items measure different constructs. If item responses from a multidimensional questionnaire are summed to give an overall measurement, it can be difficult to understand exactly what that measurement represents. For example, if a questionnaire combined items about nausea and fatigue, a mid-range score could be achieved with a high level of nausea and low level of fatigue, a high level of fatigue and a low level of nausea, or a moderate level of both constructs. Psychometric models generally assume unidimensionality and aim to measure each construct on its own scale. Several statistical methods have been described for assessing dimensionality. These include factor analysis [10], principal component analysis [11], and Mokken analysis [12].

Another important assumption is measurement invariance across different patient groups. In other words, the items must behave in the same way, regardless of differences in sample sex, age, culture, or clinical phenotype. When items do not exhibit measurement invariance, it is known as differential item functioning (DIF) [13]. One common illustration of DIF is an item about tearfulness in a questionnaire about depression—respondents who identify as male typically report tearfulness at higher levels of depression than respondents who identify as female. Another example might be asking whether someone needs assistance to use the toilet in a PROM that measures physical functioning. In this case, respondents will answer differently depending on whether they use squat toilets or western toilets.

Responses to different items in a unidimensional questionnaire should only correlate because they measure the same latent construct. The responses to one item must not be contingent on the responses to another, and two items should not be related by any reason other than that they measure the same construct. This can be assessed by measuring the residual covariance of item responses. This is the covariance that exists between the responses to two items, after accounting for the covariance that exists due to the latent construct. The term local dependence (LD) is used to describe item responses that share a high residual covariance, and this is typically measured using Yen's Q3 statistic [14]. Items that demonstrate LD may be very similar, dependent on each other, or unintendedly measuring a second latent construct. A high degree of LD will spuriously inflate reliability statistics.

9.4 Measurement Along a Linear Continuum

When thinking about information derived from modern test theory, it is useful to consider the latent construct as existing on a continuum spanning from the lowest to the highest possible amount of that construct. To aid our understanding, we could give values to the extreme poles of this continuum—0 to the lowest value and 100 to the highest. Consider a continuum of cognitive ability (Fig. 9.1).

Cognitive ability, like all abstract constructs which can be measured using PROMs, exists on a continuum from the lowest possible ability to the greatest. Modern test theory will allow researchers to know the level of the underlying continuum that the questionnaire can accurately measure, illustrated by (a) in Fig. 9.1. Additionally, modern test theory will describe the level of cognitive ability that the individual item measures (shown by (b) in Fig. 9.1). Finally, modern test theory analyses will generate an estimate of the cognitive ability of the individual that has completed the questionnaire. So, we may know that the questionnaire we have is very good at measuring people in the range of 10–70 on our hypothetical continuum of cognitive ability (a), a single question from that assessment may excel at measuring small differences between people in

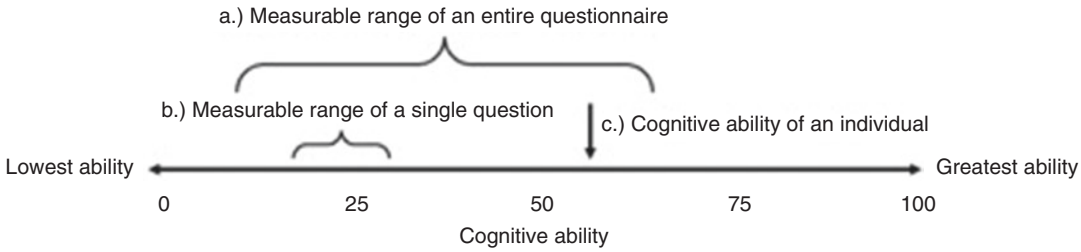

Fig. 9.1 A continuum of cognitive ability with the information available to researchers who have calibrated a questionnaire using modern test theory

the 20–30 range (b), and an individual that we have assessed using the PROM may have a cognitive ability of 56.5 (c).

An optimal PROM would assess the latent construct across a broad range of the continuum as well as providing high sensitivity to detect small changes for individuals. This provides a difficult challenge—how do we create an instrument that is both broad and sensitive, without creating questionnaires that are too long and burdensome? Computerized adaptive testing is a technique which can create dynamic, individualized assessments by iteratively selecting the most relevant items to administer based on estimates of the level of the underlying construct.

9.5 Computerized Adaptive Testing

Computerized adaptive testing algorithms comprise a minimum of three parts: score calculation, item selection, and a stopping rule. Each time the respondent answers an item, their score is calculated based on their response and the item properties described by modern test theory. Scores are recalculated with increasing confidence (decreasing measurement error), each time an item is answered. Items are selected based on their ability to measure small differences in the area of the continuum where the respondent is expected to lie, based on their score so far. In the case of the first item, this can be selected based on its ability to measure sensitively in the part of the continuum where most respondents are expected to fall. The process of item selection and score calculation continues iteratively until a stopping rule is met. This could be a prespecified number of items, a time limit, an acceptable measurement error, or a combination thereof [15].

Compared to standard fixed-length PROMs, CAT performs exceptionally well both in improving the accuracy of these assessments and by substantially reducing the number of questions needed to be asked. It is not uncommon for assessments using CAT to be more than 50% shorter than the full-length assessment [16]. The use of CAT means that a large bank of items that cover the breadth of a continuum can be developed, but only those relevant to a respondent are administered. This approach can deliver board, sensitive, low burden assessment.

There are several software options for administering CAT. These include two open-source tools which can be used for free—Concerto [17] and mirtCAT [18]. Both tools utilize the R Statistical programming language. They can be used to administer any CAT assessment with a range of options for altering the graphical layout of the PROM and, in the case of Concerto, create individualized feedback reports and interoperate with electronic health records.

9.5.1 Computerized Adaptive Testing in Cancer

Arguably, the most well-known initiative to deploy CAT in clinical practice and research has been the Patient Reported Outcomes Measurement Information System (PROMIS), which has received over $30 million in funding from the National Institutes of Health [19]. The PROMIS system uses large banks of items that

have been calibrated using modern test theory. The most appropriate items for an individual are selected using CAT. These assessments continue until a prespecified measurement error has been reached or until 12 items have been administered (whichever comes first). Results are presented as standardized T scores, usually with reference to population norms. PROMIS CAT assessments are available for a wide range of latent constructs relevant to cancer, including depression, anxiety, fatigue, cognitive function, and physical function.

The European Organisation for Research and Treatment of Cancer (EORTC) working group is also aiming to harness the potential of CAT to measure quality of life in cancer (see also Chap. 5, this volume). The EORTC-QLQ-30 is one of the most commonly used, multidimensional, quality of life measures for cancer [20]. It contains 30 items measuring 15 latent constructs. The EORTC working group has developed item banks for each of these domains (262 items in total) to be administered as CAT assessments. At the time of writing, these instruments are in the final stages of development.

There have also been initiatives to develop disease-specific CAT assessments in cancer. For example, the BREAST-Q Breast Cancer module contains a number of questionnaires to measure latent constructs that are considered important to those undergoing treatment for breast cancer (e.g., cancer worry, sexual function, and satisfaction with breast appearance). The BREAST-Q has been developed with Rasch measurement theory, meaning all of its subscales could benefit from CAT. Initial research has shown that the 16 items 'satisfaction with breasts' questionnaire could be reduced to a mean of 4 items through CAT, while maintaining satisfactory measurement error [21].

9.6 Conclusion

Modern psychometric techniques are enabling higher quality, lower burden, and health measurement within cancer. We are now able to accurately measure important latent constructs as tangibly as tumor volumes or blood marker concentrations. These measurements capture the patient's perspective in health assessments and are revolutionizing patient-centered care, research, and clinical commissioning. CAT is likely to play a key role in facilitating the uptake of PROMs by improving measurement accuracy and reducing assessment burden.

9.7 Questions That Can Be Used for Learning/Testing

1. What are the benefits of CAT over traditional PROMs? When might it be particularly helpful to apply CAT?
2. Why can CAT only be applied to PROMs that have been calibrated against modern psychometric models (such as those described by Rasch measurement theory and item response theory)? What are the assumptions of these models?
3. What are the three essential elements of a CAT algorithm? How do they interact with each other?
4. What methods can be used to determine the number of items administered by a CAT algorithm?

9.8 A Topic for Discussion That Can Be Used in Teaching

While many studies have described the benefits of CAT in health care, relatively few CAT algorithms are used routinely in care delivery or clinical research.

Electronic CAT assessments should facilitate the use of PROMs in health care. Electronic PROMs have the potential to interoperate with electronic health records, which is timelier than copying pen-and-paper scores into medical notes and avoids potential transcription errors. Remote PROM administration (via websites or smartphones) can be incorporated into the clinical workflow, potentially streamlining service delivery. In addition, CAT can reduce assessment burden from the patient's perspective.

But CAT is burdensome to introduce in clinical practice. It often requires the implementation of a separate data capture platform. This can add to clinical and administrative workloads and increase costs.

What do you perceive as the greatest barriers and facilitators to using CAT in clinical practice and research? Why has the PROMIS initiative been widely implemented while many others have not?

9.9 Further Reading List

This chapter presents a summary of psychometric properties and statistical considerations for quality of life (QoL) questionnaire validation. However, we invite interested readers who need more details to read the following books:

- van der Linden WJ, Hambleton RK (eds.). Handbook of modern item response theory. Springer; 2013.
- Wainer H, Dorans NJ, Flaugher R, Green BF, Mislevy RJ. Computerized adaptive testing: a primer. Routledge; 2000.

9.10 Research in Context

The World Health Organization Quality of Life questionnaire was developed in 1994 by an international working group. The goal of the questionnaire was to create a measure that was universally relevant regardless of whether a person had an illness or what country they were living in. The WHO group was interested in measuring *subjective* QoL—that is a person's appraisal of their life without specific objective quantification of elements of their life such as their wealth or physical health. This is opposed to health-related QoL, which may attempt to quantify the severity of illness (e.g., to ask "how far can you walk") and use that as a marker of a person's QoL. For example, in a subjective QoL measure, a person may be asked to evaluate their satisfaction with their physical ability, without declaring what their physical ability level actually is.

The original questionnaire was developed using data from an international population which included people with and without cancer diagnoses. The questionnaire was designed in two forms—the WHOQOL-100, a 100-item measure of quality of life, and the WHOQOL-BREF, a 26-item short-form version (see also Chap. 3, this volume). In both versions, scores are assessed across four domains—physical, psychological, social, and environmental QoL. In this study conducted by Gibbons and colleagues [16], the researchers sought to use the data from the WHOQOL-100 international field trial to develop brief and accurate computerized adaptive versions of the WHOQOL-100.

The researchers calibrated the scale data to the Rasch measurement model and assessed the item response theory assumptions of item independence, unidimensionality, and scalability. Of the 100 items in the original WHOQOL-100, 40 could be fitted to the Rasch model and were used to simulate CAT.

In their analysis, the researchers simulated CAT assessments with stopping rules designed to match the reliability provided by the original WHOQOL-100 and the WHOQOL-BREF. When matching the reliability of the assessments, the researchers found that the CAT versions of the WHOQOL were between 45% and 75% shorter than the original fixed-length versions.

The CAT version of the WHOQOL was developed into an online research tool and used to collect QoL information from more than 15,000 research participants from over 100 countries. The estimated time saving for this research sample of using CAT versus the long-form WHOQOL-100 is equivalent to 130 days.

Further research conducted by the group evaluated the ability of the WHOQOL-CAT

to create accurate and comparable assessments of QoL in different cultures. They assessed differential item functioning between the United Kingdom (UK), Russia, Zimbabwe, and India. They found that, despite the intention to make the measure globally relevant, some questions were interpreted differently in different countries. For example, questions relating to a person's satisfaction with their energy were related to higher levels of QoL in Russia and the UK than they were in India and Zimbabwe. This finding indicates that people in India and Zimbabwe placed less emphasis on their level of energy when thinking about their QoL than people from the UK and Russia do. The researchers provided a solution which allowed for differences in calibrations to be made to each CAT item bank in order to create assessments between these four cultures which are both sensitive to the nuances in interpretation of QoL as well as directly comparable.

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Part III

Best-Practice Elements When Assessing Quality of Life

10 Statistical Considerations in Analyzing Health-Related Quality of Life Data

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A. Kassianos (ed.), *Handbook of Quality of Life in Cancer*,
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10.1 Introduction

Information about health-related quality of life (HRQoL) plays a central role in evaluating therapies, providing population-level surveillance, and informing patient-provider decision making in oncology settings. Many HRQoL instruments are patient reported; however, the term "patient-reported outcomes" refers to a wider group of health outcomes reported directly from the patient. Understanding HRQoL in cancer patients is most effectively done through PROs directly measuring disease symptoms and functioning. PROs are a type of clinical outcome assessment (COA) along with clinician-reported, observer-reported, and performance outcomes.

We use the term PRO throughout this chapter although most of the statistical considerations are also appropriate for any type of COA measure. In fact, many analytic approaches for patient-reported outcomes are no different than other health measures with similar numeric attributes. However, because of both the subjective nature of patient-reported data and desire for results that are easily interpretable to a wide range of stakeholders, we discuss statistical considerations of PROs to assess HRQoL in cancer patients in any variety of research settings.

This chapter will enable readers to (a) understand properties of PROs to consider, including scoring, used in oncology studies; (b) form an appropriate research objective; (c) understand frameworks of missing data in oncology studies; (d) design basic longitudinal analyses; (e) formulate endpoints and analyze data for optimum interpretability; and (f) design graphic representation of results from health-related quality of life data.

10.2 PRO Properties

PRO instruments are designed to measure patient-reported constructs, also called domains. Types of PRO instruments include PRO questionnaires, diaries, and numeric rating scales, all of which can be captured on paper or electronically. Development of valid and reliable instruments is an important process covered elsewhere in this book and in others [13] (see also Chaps. 4 and 7, this volume). Here we assume that PROs are measured with psychometrically sound and fit-for-purpose instruments.

A first step in deciding which statistical procedure to apply to PRO data is to understand the numeric properties of the measure. PRO instruments record patient experience through items with standardized sets of response options. Items are most often questions but can also be statements or even a task. Simple concepts might be measured in as few as one item, while more complex concepts require multiple items which are scored together and called a domain (or sometimes scale). Many PRO instruments aggregate multiple items, often through summing, for a domain score representing a single construct. While theoretical challenges exist on the appropriateness of combining ordinal items for a composite score [15, 31], it is nonetheless a common practice defendable through psychometric validation.

Items using ordinal response options are common on PRO instruments. Ordinal responses have an ordered and unique meaning assigned to each value although the size of the interval between categories may vary. An example is "much improved," "minimally improved," "no

change," "minimally worse," and "much worse." Each category has a rank-ordered numeric value used for scoring. Numeric rating scales are another common type of PRO item, similar to ordinal scales with the additional attribute of equal intervals with reference to the size of the difference between each level. One can assume that the difference between a rating of 5 and 6 is the same as the difference between 1 and 2.

Scoring instructions should note items that need to be "reversed coded" so that the degree of impact is measured in the same direction. For example, a high score could represent a high (positive impact) level of function or a high degree of bother (negative impact).

10.3 Developing the Research Objective

Statistics are tools that help us answer research questions. Questions can draw on the attributes of the natural history of the cancer, past patient experience, known treatment toxicity, or issues with clinical management of the disease, for example. Robust patient- and clinician-relevant results should arise from well-defined research questions accompanied by well-designed studies and appropriate statistical approaches. The current emphasis in the literature on estimands, as described in the next section, originated from clinical trial settings though the concepts and attributes will easily translate to other types of longitudinal studies using PROs.

10.3.1 The Estimand Framework

The lack of clear research objectives in the regulatory setting resulted in difficulty interpreting PRO results [21, 44]. For clinical trials, the estimand framework provides a structure to align a research question with the study design, conduct, and statistical analysis. The International Committee on Harmonisation ICH E9(R1) addendum defines an estimand as what is to be estimated [33]. In brief, the estimand framework begins with the research question and encompasses five attributes: the treatment patients receive, including any comparator; the study population of interest; the variable or endpoint; the definition of intercurrent events (ICE); and the population-level summary or statistic. Intercurrent events are events that may happen post-randomization and can affect the analysis and interpretation of the outcome. In cancer trials with a PRO endpoint, intercurrent events can include, for example, disease progression or treatment switching. More technical explanations of the estimand framework, including five analytic strategies, are available for clinical trials in general [41, 45] as well as PRO- and oncology-specific trials [7, 21, 35].

10.3.2 SISAQOL Taxonomy of Research Objectives for Trials

Setting International Standards for the Analysis of Quality of Life (SISAQOL) consortium supports a taxonomy of research objectives for PROs in oncology trials [15]. Specifically, research objectives should be tailored to the PRO domain and encompass four attributes. The first delineates whether the purpose is to quantify a treatment effect or describe the patient experience. Second, the objective should designate the between-arm comparison of the PRO to be superiority or non-inferiority, as analyses and interpretation differ. For example, a non-statistically significant result of a superiority hypothesis should not be interpreted as a treatment effect that is equal or not worse [46, 53]. Consider an oncology trial designed to test superiority with a primary clinical endpoint of time-to-progression. It may be hypothesized within the same indication and population, however, that the investigational arm toxicity profile is no worse than standard of care. Here, a non-inferiority PRO objective is appropriate.

The third attribute relates to the hypothesized within-treatment group directional assumption. Patients might be expected to experience improvement (e.g., on functional status), remain stable or deteriorate (e.g., on disease-related

symptoms through progression). Lastly, population-level summaries should reflect whether the PRO objective is within-patient (e.g., describing patients who have achieved a meaningful PRO change) or between treatment arms.

10.3.3 Research Objective Example

Consider a simulated dataset to represent a two-arm, equally allocated, randomized controlled clinical trial ($N = 200$) in renal carcinoma with a PRO endpoint measuring patient fatigue monthly at baseline through month 3. Consider fatigue measured using a multi-item, single-domain PRO instrument scored from 0 (least severe) to 100 (most severe). Below is the research question for this fictitious example (Table 10.1). When the research question is stated as a whole, most elements of the estimand are contained within. The hypothesis type and directional assumption are denoted when specifying more score improvement in one arm versus the other. The population is defined by the study protocol, and since there are no additional exclusions, the research question applies to the full trial population. The phrase "regardless of disease progression" directs the handling of assessments measured after disease progression, the defined ICE. In contexts where death due to disease is likely to be a factor, the handling of such (missing) data is important to define through the ICE and within the statistical analysis plan.

Table 10.1 A PRO research objective using estimand and SISAQOL attributes in the context of oncology clinical trials

Attribute	Research objective
Research question	Does the average change in fatigue symptom score improve more in the intervention arm compared to the comparator arm 3 months post-intervention, regardless of disease progression?
Hypothesis type	Superiority
Treatment	Two arms: Interventional product Comparator product
Population	Adults with renal cell carcinoma and defined by the study inclusion/exclusion criteria
Variable	Change from baseline on the fatigue score at month 3
Directional assumption	Improvement
Intercurrent events (ICEs)	Disease progression: assessments post-progression used in analysis
	Missing for other reasons: handled implicitly by the analytic model
Summary measure of variable	Mean comparison within treatment arms

10.4 Multiplicity

Oncology studies are often designed to evaluate many facets of disease including symptoms, toxicity-related side-effects, and the effects of disease or treatment on physical function and well-being. Perhaps unlike a biomedical response that might be measured with a single value, the patient experience is often characterized through multiple attributes each measured through separate endpoints. For example, the FACT-Cog measures cognitive function through the following subdomains: Perceived Cognitive Impairments, Impact of Perceived Cognitive Impairments on QoL, Comments from Others, and Perceived Cognitive Abilities [57].

In frequentist theory, statistical evaluation is based on testing hypotheses. For a superiority objective, the rejection of the null hypothesis suggests that there is a difference between study groups. There is always the possibility of falsely rejecting the null when the null is true, defined as a type 1 error. Moreover, the chances of experiencing a type 1 error increases when evaluating multiple endpoints, known as the familywise error rate. This happens when multiple statistical tests are performed without adjusting for the fact that the probability of rejecting for least one or more true null hypotheses increases. Multiplicity issues can occur with multiple endpoints, with repeated testing of the same endpoints at different timepoints, when comparing multiple groups or any combination thereof.

One principled way to address multiple PRO endpoints is to specify only the domains that are

expected to show treatment differences (or in the case of a non-inferiority hypothesis, be no worse between the groups) [50]. When several endpoints are relevant, multiplicity adjustments can be made by adjusting the alpha value prior to testing each null hypothesis. The Bonferroni adjustment is the most well-known of these. Step-wise tests predefine the sequence of endpoints testing using a combination of importance and likelihood of success to control the familywise error rate. Examples include the Bonferonni-Holms procedure and the Hochberg method [29, 30].

The practice of adjusting for multiple comparisons can vary substantially by field and setting. In general, studies that will be used for decision making are good candidates for multiplicity adjustments, while those that are hypothesis-generating may not be. Nonetheless, the authors suggest adhering to a predefined statistical analysis plan in most settings to avoid phishing for significant results. In the context of oncological pharmaceutical development, PRO endpoints are often positioned as secondary or exploratory. For the latter, inferential statistics may be calculated without hypothesis testing. There is growing recognition of the multiple assessments necessary to fully evaluate a products benefit and the need to consider alternatives to hypothesis testing and p-values [26]. A similar approach can be used in observational studies where modeling of outcomes may be more exploratory or iterative in nature.

10.5 Missing Data

Oncology studies are often longitudinal in design, assessing patient's HRQoL status one or more times after the start of the study, which results in missing data when someone does not return for a study visit or assessment, withdrawals from the study, or misses PRO assessments for other reasons. Missing data is common and a nearly evitable consequence of longitudinal data collection [5]. Missing data will at best reduce power to find statistical differences when they exist, and at worst, bias results leading to incorrect conclusions. In other instances, data may not be missing but could be excluded from an analysis if not relevant. An example could be PRO assessments collected post-disease progression when the research question is to understand the effect of an intervention prior to progression. Note that certain data might not be included in the analysis for one research question but included for another; it would be unethical to collect data without intent of use.

As we explain in the following sections, the handling of missing or irrelevant data and the choice of analytic procedures need to be jointly considered. Advances in methods of handling missing data and the impacts of those choices on the interpretation of results have highlighted the need to consider missing data at all stages of research [3, 38]. Starting with study design, prevention of missing data should be a key goal rather than relying on statistical methods, which can carry strong unverifiable assumptions about the nature of the missing responses, to model unbiased results. PRO data can be missing because of known reasons (the patient dies, their disease progresses and is not collected, or they are too ill to complete the assessment) or unknown reasons (the patient did not show up to their scheduled assessment, was not offered their questionnaire from study personnel, or provided incomplete PRO assessments).

How much missing data is too much? It would be convenient if a clear threshold existed. Researchers may suspect biased results if the missingness is disproportionately from one group, whether a treatment or intervention arm, a group defined by a baseline characteristic, or disease severity, for example [9]. It is reasonable to assume that small proportions of missing data might have minimal effects on estimates. However, as the amount of missing PRO data increases and the type of missing data varies, confidence in the accuracy of inferences erodes.

10.5.1 Item-Level Missing Data

For PROs, missing data can be on some items in a multi-item instrument or the entire instrument. Established oncology PROs, including those in

The European Organisation for Research and Treatment of Cancer (EORTC) and Functional Assessment of Cancer Therapy (FACIT) measurement systems, have published scoring rubrics indicating how many items can be missing in the calculation of a domain score (see also Chaps. 5 and 6, this volume). A common example of a scoring rubric is to average the scores of the available items if a minimum number of responses are available [20]. This approach is algebraically equivalent to imputing missing items as the average of the observed items within the domain.

The 'half-item' rule may be used in absence of published scoring rules, although the level of potential bias is dependent on the pattern of missingness within the items. Mean imputation when half of the items are answered is reasonable when the item-correlation totals are similar and the domain has high internal consistency as measured by Cronbach's alpha [25]. For example, items may be skipped randomly if a participant loses a page of the instrument. On an instrument with high internal consistency, the 'half-item' rule would be unbiased. Item-level incompleteness is not completely random if patients are more likely to skip items that are related to, say, severity of a symptom. This could happen if patients who experience sexual dysfunction are less likely to answer questions about this condition, underestimating the overall symptom burden. Nonetheless, the benefits of preserving sample size may exceed issues of (relatively low) bias leading some researchers to further suggest relaxing the 'half-item' rule if the purpose is to evaluate summary measures rather than individual response [4].

Another statistically principled approach to scoring domains when a portion of items are answered is to use multiple imputation. Researchers can either multiply impute missing items prior to scoring the domain or impute the score itself. Multiple imputation (MI) replaces missing (item or domain) values with a set of plausible values drawn from the conditional distribution of missing given observed values repeated M times. The next step is to analyze the M datasets containing a combination of observed and imputed values. One fundamental feature of combining imputed datasets is that the uncertainty of the missingness is reflected in the pooling of the standard errors [49]. Commonly refered to as Rubin's rules, the variance estimator is an intuitive combination of the within- and between-imputation variability. Imputation performed at the item level, as opposed to the domain, is more efficient when other items within the domain are used in the imputation model because these items are often stronger predictors of item response than are other covariates, such as demographics or clinical attributes [24]. However it is unclear the best way to account for the uncertainty of missingness if item values are imputed prior to scoring the domain. Treating domain scores as missing if at least one item response is missing and using all domain items in the imputation model circumvents this problem while maintaining the efficiency of item imputation [42].

When entire PRO assessments are missing for known or unknown reasons, we consider the research question and the mechanisms of missing data to choose an approach for statistically modeling outcomes. PRO assessments can be missing intermittently, where a patient might be missing one assessment but subsequent assessment(s) are observed, or in a monotone pattern with no observations after a specific timepoint. We briefly describe Rubin's taxonomy of missingness in the context of PROs [19, 39].

10.5.2 Missing Completely at Random

Data are said to be missing completely at random (MCAR) if the probability of missingness, conditional upon covariates, is not related to observed or unobserved PRO responses. In other words, the probability of missing responses is not related to the outcome. In a clinical trial setting, the effects of randomization are preserved when data are truly MCAR; however, in most settings this is considered an unrealistic assumption. Methods relying on an MCAR assumption should be interpreted with caution in the presence of missingness.

10.5.3 Missing at Random

Data are considered missing at random (MAR) if the probability of missingness, conditional upon covariates and observed outcome data, does not depend on the unobserved outcome responses. In practice, this means that the missing PRO outcome depends only on the observed data, not the missing data after conditioning on covariates. With longitudinal data, the patients' past responses are assumed to predict their missing responses.

10.5.4 Missing Not at Random

Lastly, data are considered missing not at random (MNAR) if the probability of missingness depends on the missing data. MNAR analyses rest on the strongest assumptions since any data that would predict the missing response is in fact missing. More detailed explanations and examples can be found in [13] and [19].

We caution the use of any approach that uses only complete observed cases including *t*-test and analysis of variance (ANOVA) including extensions such as repeated measures and multivariate ANOVA in the presence of missing data. Estimates will be unbiased, albeit statistically inefficient, only if data are MCAR. In oncology settings, this is rarely the case; complete case analysis can underestimate symptomatic toxicity and overestimate HRQoL increasingly over time. Of note, complete case analyses defies the intent-to-treat principle of clinical trials where all patients are analyzed according to the arm which they were randomized.

10.5.5 Describing Patterns of Missingness

Oncology studies are often lengthy, with multiple PRO assessments, and vulnerable to missing data. This is especially true in settings where symptomatic toxicity is severe, or large proportions of patients progress or die. One strategy in understanding levels of known and unknown missingness across the assessments is to report patient PRO missingness disposition. A disposition table or bar chart reports the proportions of patients who are missing due to the various reasons, including PRO completion.

Comparing demographics and other clinical characteristics for patients who do and do not drop out stratified by intervention arm for trials or exposure for observational studies can give indication of the extent that missingness might influence inferential statistics and generalizability. Further, such an analysis can identify variables associated with missingness to be leveraged for use in multiple imputation models.

For longitudinal studies, graphical representation of the PRO score over time stratified by treatment arm or comparison groups and by when participants are no longer observed, e.g., due to death or attrition, is another way to understand how missingness can affect estimates.

Consider again the clinical trial described in Sect. 10.3.3. If the trajectories over time differed substantially according to when patients dropped out, then data are not MCAR. Figure 10.1 shows that those who dropped out started with lower baseline PRO scores compared to those who remained in the study. In the treatment arm, the direction of the trajectory patterns differs for those who were completely observed and those who were not.

Specifying how missing or unobserved data are handled, including those for known, e.g., progression, and unknown reasons, is an important component of the plan to evaluate the research question. In trial settings, the estimand framework defines the handling of intercurrent events, which may include handling of unobserved data particularly when an ICE like disease progression results in missing observations. As we will see in the following sections, the ways in which either intercurrent events or missing data are handled, in combination to the modeling approach, will influence the interpretation of the PRO estimate.

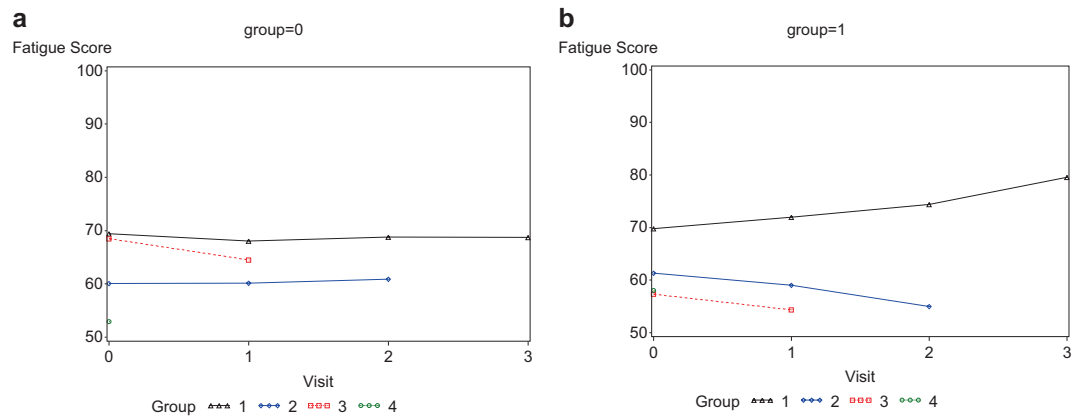

Fig. 10.1 Missingness patterns: Fatigue score stratified by treatment groups (**a** and **b**) and dropout time. The possible range of Fatigue is 0 to 100, with higher values indicating better outcomes

10.6 Sensitivity Analyses

Both in and outside of the regulatory setting, there is growing support for sensitivity analyses on PRO endpoints [2, 17, 55]. Sensitivity and primary analyses generally use the same endpoint, but sensitivity analyses usually use a different statistical approach. Most statistical assumptions of missingness cannot be verified, and agreement of results between the primary and sensitivity analyses can provide a level of confidence to the robustness of the primary analysis results. The goal is to understand the extent to which the estimates rely on the analytic approach and assumptions of missingness. If sensitivity analysis results do not change much from the primary analysis, researchers and others can be confident in the conclusions.

Specific to PROs, sensitivity analyses should include alternative methods of addressing missingness from items missing within a domain or when entire domains are missing [2, 13].

10.6.1 Longitudinal Analysis of PROs

PROs are often assessed repeatedly on the same patients and can characterize within- or between-group comparisons. In the study design phase, the frequency and timing of assessment must coincide with the recall period of the PRO as well as hypothesized timing of symptomatic or functional changes [19]. In cancer studies, treatment initiation may illicit symptomatic toxicities in the short term that wane in severity post treatment. For example, improvement in functional status may not be expected until months into the study. The repeated assessments of PROs allow for characterization of response over time.

Practical and statistical issues complicate the analysis of longitudinal data. Multiple assessments on the same people produce correlated data, violating assumptions of independence necessary for basic statistical tests. Data may be missing or may be collected at irregular time intervals. Usefully, longitudinal models are flexible enough to accommodate these and other scenarios; however, choosing the most appropriate model and interpreting results correctly can be confusing. This section will briefly cover some of the most common modern techniques used in cancer studies. Reference for more compete and technical explanations include [19] and [22].

Longitudinal models fall into two broad categories: generalized estimating equations model (GEE) and mixed models [37, 56]. Both sets of models can accommodate continuous and ordinal dependent variables. Both allow for time-invariant predictors which have a constant value for each participant over time, e.g., gender, and time-varying predictors which can change over time. A key feature of longitudinal models is the ability to model within-subject correlation from

the repeated measurements. In this chapter, GEEs are described in Sect. 10.7.3. in the context of binary outcomes.

Time can be used as a discrete or continuous variable in mixed models. If PRO assessments occur at varying intervals or if the interest is in the difference in the averaged group means over time, time should be treated as a continuous variable. These models may be referred to as growth-curve models and often include terms beyond linear to appropriately model the relationship between time and the outcome. When time is considered discrete and the within-subject covariance matrix is unstructured, these models are generally referred to as mixed models for repeated measures or MMRMs [40]. Estimates for between-group mean differences can be extracted at any timepoint including the end of the study with the inclusion of a time by group interaction. In either specification of time, subjects may have different number of follow-up assessments. Parameters are estimated through maximum likelihood and are unbiased if data are MAR. This implicit imputation of missing data through a MAR assumption is a convenient feature likely contributing to the popularity of this approach.

10.6.2 Longitudinal Analysis Example

We simulated a dataset according to the design of the previously described trial with a PRO endpoint measuring fatigue, $N = 200$. After generating the data, we omitted 28 (14%), 39 (20%), and 52 (26%) responses at the first, second, and third post-baseline assessments to model attrition under a MAR assumption where observations were more likely to be missing if PRO scores were lower at previous timepoints. This resulted in the following group mean vectors:

- Intervention arm: 67.0 (SD = 15.6), 70.4 (SD = 15.5), 72.9 (SD = 14.5), and 79.6 (SD = 13.3), for baseline and three follow-up measures reflecting, on average, improving scores over time
- Comparator arm: 66.3 (SD = 14.2), 66.8 (SD = 11.5), 67.6 (SD = 11.1), and 68.8 (SD = 12.5), for baseline and three follow-up measures modeling no intervention effect on fatigue.

The repeated within-person correlation was 0.7 replicating a compound symmetric covariance structure.

We evaluated the research question: *Does the average change in fatigue symptom score improve more in the intervention arm compared to the comparator arm 3 months post intervention, regardless of disease progression?* using all available data (regardless of progression status) in an MMRM model. Specifically, the difference in mean scores was analyzed using a restricted maximum likelihood (REML)-based repeated measures approach as implemented in SAS Proc Mixed. The model included the fixed, categorical effects of treatment, visit, and treatment-by-visit interaction, as well as the continuous, fixed baseline score. The within-subject errors were modeled with an unstructured (co)variance structure, and the Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors.

The least-squares (LS) means for the treatment and comparator arms at the final assessment was 77.2 (SE = 1.45) and 66.2 (SE = 1.46), respectively. The difference of LS means at the final post-baseline assessment was −10.7 (SE = 2.06, 95% CI: (−14.7, −6.6)), $p \leq 0.0001$. The higher post-baseline mean score of the intervention arm and the negative difference demonstrates a greater magnitude of improvement in the treatment arm as compared to the control arm, regardless of disease progression.

10.7 PRO Endpoints for Interpretability

As HRQoL evidence is being increasingly used to support oncology regulatory and clinical decision making, there is a simultaneous need to improve interpretation of patient-reported data [11, 15]. PROs quantify latent concepts,

such as fatigue or pain, measured via various established or occasionally newly developed instruments. There is no universal scale for which to attach meaning of a change score, like kilograms for body weight. For example, an instrument may be scored from 0 to 30, while another 0 to 100. Some PROs are normed to have a general population average of 50. Worse, the direction of severity is not consistent. High scores may represent severity of the condition or more of the outcome. But "more" physical function is better, while "more" symptom burden is not. The variation in the way in which these latent concepts are measured complicate understanding of PRO scores. We attempt, through interpretable endpoints, to attach meaning to the values of PRO results so that users of these data, including regulatory bodies, healthcare policy decision makers, and individual patients, can understand the patient experience.

There are efforts to standardize common PROs used in oncology settings, including Patient-Reported Outcomes Measurement Information System (PROMIS) Network, part of the National Institutes of Health Roadmap Initiative, and the Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events (PRO-CTCAE) item banks. PROMIS measures are publicly available, psychometrically validated, precise, and cover the most common patient-reported domains, as well as cancer-specific domains. The PROMIS measures scores are standardized making them comparable with across domains and even with other measures, increasing interpretability. Still, such common measures are not used universally to the envisioned potential.

10.7.1 Standardized Effect Sizes

Interpretation of PROs is complicated not only by different scales and direction of severity but by the use of multiple measures within or across studies. A recommended approach for reporting multiple PROs in oncology studies comparing treatment or intervention groups is to standardize and graphically display results [6]. Standardization of mean group differences of PRO scores (raw or model-adjusted) puts the units of measurement on the same scale, stripping the need for an intrinsic meaning of the scale units so that group comparisons can be made across multiple domains. One way to achieve this is through a standardized effect size (SES) where the mean difference is divided by the standard deviation of either or both means. The result is transformed to a *z-score* which has a mean of 0 and variance of 1. For example, Cohen's d uses the pooled standard deviation, a weighted combination of both groups' standard deviation, although other versions of pooled standard deviations can be applied such as Hedges' g [16, 28]. Cohen's d is often interpreted as small, medium, and large for $d = 0.2$, 0.5, and 0.8. Confidence intervals (CIs) for SES are derived from non-central t distributions.

SESs from multiple PRO domains can be displayed as a forest plot providing a comprehensive visualization of the magnitude of differences in treatment groups in a single graphic. Including the corresponding 95% CIs suggest statistical significance at $p \leq 0.05$ if the values do not include 0. For example, an RCT of a web-based psychosocial intervention aimed to increase cognitive function in cancer survivors had a primary endpoint of improved cognitive function measured by the perceived cognitive impairment domain of the FACT-COG [12]. Standardized treatment differences from 11 other PRO domains including additional measures of cognitive function; measures of physical, social/family, emotional, and functional well-being; stress, anxiety, and fatigue were reported in a forest plot [6]. Each PRO domain was listed along the y-axis with two symbols indicating SES values post-intervention and at 6-month follow-up to assess sustained benefit. Notches along the x-axis note the small, medium, and large SES sizes in the positive and negative directions. A solid vertical line at SES = 0 as well as segmented lines at −0.5

and 0.5 provide visual references of SES magnitude. Labels along the x-axis indicate if the direction of SES favors the intervention or control arm.

10.7.2 Statistical Significance, Clinical Significance, and Patient Relevance

Inferential statistics can use a p value to quantify the probability that the observed, or a more extreme, result is due to chance if the null hypothesis were true. Usually set at $p \leq 0.05$, a statistically significant result suggests with a 1 in 20 chance of being incorrect is valid. However, a statistically significant results does not in and of itself provide information on the magnitude of the result or clinical importance. Indeed, a small difference between groups may be statistically significant owing to a large sample size and power, for example.

The practice of determining the amount of change that matters is not new, however views, particularly in the regulatory setting, have evolved. Currently, the preferred patient-relevant threshold is derived from and applied to within-person change values, referred to as the within-person meaningful change threshold (MCT) [32, 55]. Anchor-based derivation, relying on correlated external measures to determine the value of within-person change on the PRO score that corresponds to a meaningful magnitude of change on the external measure, is usually used. Appropriate derivation, not covered here, accounts for the idea that the minimum detectable amount of change does not necessarily correspond with an amount of change that is meaningful to the patient, and values for deterioration and improvement may be different.

Another related and commonly used threshold is the minimally important difference (MID), also referred to in the literature as the minimal *clinically* important difference or clinically important difference. MIDs have been defined as the amount of change patients perceive as beneficial and would alter the course of treatment [34, 43]. Methodologically, MIDs are derived by comparing group-level data rather than assessing change occurring within the patient. Values are derived from the difference in mean scores between adjacent anchor categories rather than the mean change within an anchor category. MIDs were thought to provide reasonable estimates of a clinically meaningful change that could be applied both to individual patients and to understand group differences [34, 47]. When used to interpret result, the difference in mean scores between treatment arms or intervention groups would be considered clinically significant if the difference exceeds the MID. For patients making healthcare choices, these results may have limited meaning.

Other methods to determine thresholds include distribution-based approaches, receiver operating characteristic curves, and the use of standardized effect sizes, or a combination of these. For a more detailed understanding of these methods, see [13, 18, 47]. In an observational study, thresholds could be derived using data from an early timepoint, e.g., at 6 months in a 2-year study, and for a clinical trial, unblinded data can be used prior to database lock. Alternatively, there may be previously published thresholds derived in a similar population on the PRO of interest that may be suitable.

10.7.3 Quantifying Meaningful Response

Responder analysis is one way to demonstrate the clinical and patient relevance of a continuous or ordinal PRO endpoint. In its most simple form, patients are classified as responders by dichotomizing the PRO score if they improve by the MCT. Proportions of responders can be compared across groups, providing useful information to non-statistical persons.

Once again, consider the simulated renal cell carcinoma dataset from Sect.10.3.3. Assuming the MCT = 10, we categorized participants into those who have improved if their change score was equal or greater than 10. Figure 10.2 displays proportions of those who have experienced a meaningful within-patient improvement on

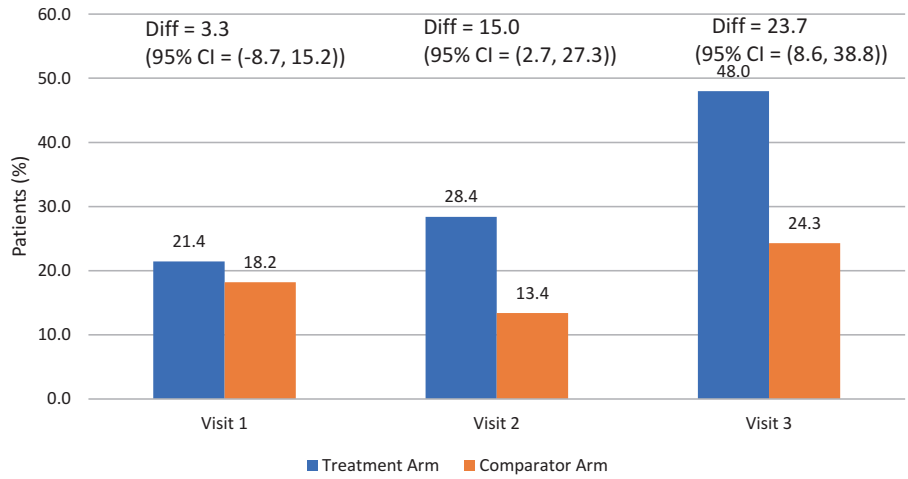

Fig. 10.2 Proportions of patients whose fatigue improved, by and between treatment arm, as defined as $a \geq 10$-point improvement on the fatigue scale

fatigue for each visit. One research question that can be answered with this analysis is: *What is the difference in the proportion of patients still enrolled in the study at visit 3 in the intervention arm compared to the comparator arm who experience meaningful improvement in fatigue?*

Results can be verbalized as, for example, "48% of patients in the intervention arm experienced a meaningful level of improvement on fatigue, compared to 22% in the comparator after 3 months of treatment." In oncology studies, interest may lie not just with responders but also those who remain stable or deteriorate. A test of proportions can evaluate statistical significance for the difference between treatment groups.

The easy interpretation of responder analysis results is appealing; however, there are limitations. The MCT is intuitive but can carry an assumption that the lowest change value will be the most sensitive to between-group differences; however, this is not always true [36]. Perhaps more importantly, transforming a continuous variable to binary leads to a loss of statistical efficiency and subsequent loss of power. In some instances, up to 50% more subjects would be required to power the same outcome if analyzed through a responder analysis rather than remaining continuous [1, 51] potentially exposing people to ineffective or toxic treatments unnecessarily. Given these concerns, responder analysis is recommended as supportive evidence for the same endpoints evaluated using parametric methods [15].

Modeling the likelihood of improvement (or deterioration) using GEEs is another readily interpretable approach evaluating responders across multiple timepoints. GEEs are a flexible family of models that can be used for normal and nonnormal outcomes, such as binary, while accounting for the correlated repeated measures across patients. Here, we use the logit link function and the binomial distribution family for the responder outcome. GEEs are robust to misspecification of the correlation structure; however, some methodologists recommend an independent correlation structure [8]. When GEEs use a binary outcome, estimates are interpreted at a population level as opposed to subject-specific models such as generalized linear mixed models for binary data.

An important consideration of GEEs is that only complete cases are used, meaning that patients' PRO scores must be observed at all timepoints. This is an unlikely scenario in oncology studies where patients may miss assessments intermittently due to toxicities, or monotonically due to disease progression, among other reasons. One approach is to code missing observations as non-responders. Composite responder endpoints that include

missing as non-response are often thought to be conservative by biasing the treatment effect toward the null. While this is true within-treatment arms, the difference between arms may be biased in either direction, potentially indicating a statistically significant treatment effect where one does not exist, a type 1 error [23]. As such, extensions of GEEs such as inverse-probability weighted GEEs and GEEs with multiple imputation, both valid when data are MCAR or MAR, may be good choices [8].

It should be noted that generalized linear mixed models can also model binary outcomes although the interpretation of the result becomes subject-specific (in the case of a binary outcomes only). Because of the maximum-likelihood estimation, these models are appropriate for MCAR and MAR data without the use of additional analytic considerations such as imputation or weighting.

10.7.4 Likelihood of Meaningful Improvement Example

Using the previously described simulated dataset, we modeled the likelihood of meaningful improvement using a GEE with MI. The articulated research question was: *What is the likelihood of meaningful improvement in fatigue in the intervention arm* versus *the comparator arm over the course of three months of treatment?*

Multiple imputation is a three-step process: use an *imputation model* to repeatedly predict values of missing observations for *m* datasets; analyze the *m* complete datasets according to your plan; and then combine the estimates in a way that accounts for the uncertainly of the missingness by correctly calculating the standard errors. The imputation model leverages the observed data to informatively impute new values, in this example, under the MAR assumption, although other applications use an MNAR assumption [14]. Imputation models can incorporate additional covariates associated with missingness that may not be used in the analytic phase.

In this example, we used the fully conditional specification which assumes conditional distributions for each partially observed variable and uses a corresponding regression model to sequentially generate imputations, e.g., linear regression for continuous variables and logistic regression for categorical variables. We used a "wide form" data structure (one row per patient) to preserve the within-subject correlation. The imputation model as implemented in SAS Proc MI included the treatment group indicator and the continuous PRO score for each visit.

Patient's responder status was calculated on the post-baseline change scores being equal or greater than 10 points (responder = 1) or not (responder = 0) using observed or imputed (if unobserved) values of the PRO score prior to applying the GEE model to the $m = 100$ datasets. The GEE regressed responder status on fixed effects of treatment arm, visit, baseline PRO score, and the interaction between treatment arm and visit. We used an independent covariance structure with no assessment of the best fit correlation matrix since GEEs are robust to misspecifications of the within-subject correlation matrix. Results suggest that the odds of improving meaningfully in the intervention arm is 2.3 (95% CI: 1.3–4.2) times the odds of improvement for patients in the comparator arm over 3 months.

10.7.5 Time to Meaningful Change

In oncology studies and commonly in clinical trials, clinical endpoints are often analyzed as a time-to-event, such as progression-free survival. Similarly, important patient-reported information can be obtained by modeling time-to-event data to estimate, for example, median time to symptom improvement. Elements of time and occurrence of a defined meaningful event are modeled together. The Kaplan-Meier estimator-derived median (and quartile) times to event with associated curves is a common non-parametric approach to modelling time-to-event, with a log-rank test to compare groups. Interpretation can be

enhanced with the hazard ratio from the Cox proportional hazards model.

In oncology studies, careful consideration is warranted in defining the event and the censoring rules. PRO events can be based on improvement or deterioration by defining improving (or deteriorating) as the magnitude of a change score at or above the MCT. Censoring is often defined as the time when the patient has reached the end of the study or no longer has observable data due to other reasons. Depending on the study design, research question, and expected natural history of the cancer, progression or other ICEs may be included as an event (deterioration only) or part of censoring. Further, patients can experience a PRO-based meaningful event at one cycle, then revert back at another. This has led to varying definitions of events, depending on primary question of interest in the study population. One endpoint is time-to-first deterioration where the event is the first cycle or timepoint a patient deteriorates [27]. Time-to-definitive deterioration of at least one MCT *without any subsequent improvements of at least one MCT* is another endpoint [10]. Here, death and progression are often considered in the event definition in a palliative setting.

10.8 Visualization

The usefulness of PRO data depends in part on the extent results can be understood by clinicians, patients, and other health-care decision makers. Graphical representation of results is a useful way to visualize patterns and trends across time and/or across numerous outcomes. Data visualizations done well will appeal to a wide range of stakeholders including those who are less proficient in comprehending and comparing values in tabular or text form (see also Chap. 12, this volume).

The variability across PRO instruments of the range of possible values and the direction of impact impose unique challenges to visually presenting PRO results. When considering a graphic, one of the most important features is to indicate the directionality of the score. This can be done with arrows and labels indicating improvement or deterioration along the relevant axis for line plots of score changes over time, or forest plots, for example. Multiple endpoints on the same graphic should be displayed in a consistent direction, e.g., higher scores equate to improving conditions. Multiple endpoints are best displayed on the same scale, see Sect. 10.7.1 on SES.

Conveying score meaning in graphics is important but not always straightforward to operationalize [52]. For example, descriptive labels such as mild, moderate, and severe could be included but only if sufficient evidence supporting such interpretation exists. In absence of established ranges for ordinal categories, graphics can indicate the extreme values, e.g., 0 for worst and 100 for best.

One particularly useful graphic to support the interpretation of responder thresholds in relation to the continuous (or ordinal) PRO outcome is a cumulative distribution function (CDF). Here, the cumulative distribution of the change score is displayed along the x-axis with improvement values to the left and deterioration to the right of 0. The y-axis displays the cumulative proportion of responders who have achieved each change score such that the ogive reads as an "S" from left to right. Note that for scales where positive change values represent improving scores, the values of the x-axis will be opposite from convention, starting from positive to negative as read from to right. Vertical lines can be added at the MCT or values for multiple MCTs [32]. For example, using the results in Fig. 10.3, we see results such as "48% of the intervention group compared to 24% of the comparator group responded to treatment at MCT = 10." In this fictitious example, we note there is consistent separation of curves along the majority of the lines suggesting that the difference in treatment arms exists not just at the defined threshold but over a range of thresholds. This is consistent with the notion that a threshold could actually exist as a range [48].

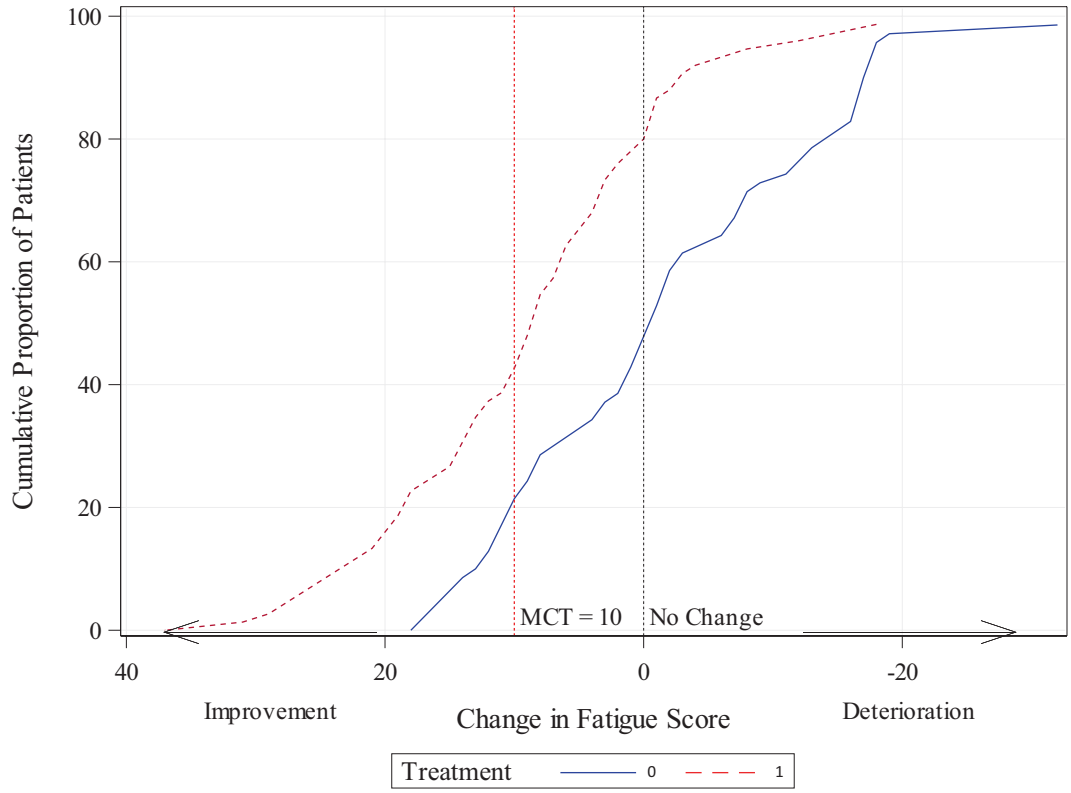

Fig. 10.3 Cumulative distribution function of fatigue change scores for two groups. Positive change scores along the x-axis indicates improvement. The solid line represents the intervention group, dashed line the control group

10.9 Summary

The patient's voice in oncology research is an important aspect for informed health decision making. Without it, patients, clinicians, and other health decision makers are unable to accurately ascertain subjective outcomes of pain, symptom burden, physical function, and overall well-being, to name a few.

Due in part to the subjective nature of the concepts being measured and the characteristics of the data itself, PRO analyses require additional considerations. A key concept is interpretability. PRO scales are often inconsistent in range and in directionality, and values lack an inherent understanding of meaning. Whether in an observational study or a clinical trial, a clearly defined research objective is a good first step to guide the analytic approach leading to understandable results.

While group-level statistics may have the most statistical power to estimate overall treatment or intervention effect, they have limited meaning at the individual level. Analyses based on a within-person meaningful change, while statistically less efficient, yield results that are easily digestible to a wide range of stakeholders.

Finally, effective graphics of PRO data summarize health-related quality of life concepts together and, when standardized to a common scale, allow for comparison across different domains or instruments.

Table 10.2 summarizes a set of research questions with related results to provide a snapshot of the patient experience of fatigue in a simulated renal cell carcinoma trial. Overall, we see that on average people in the intervention arm improved 11 points more on the fatigue scale compared to the comparator arm. The patient-relevant results reveal 48% of those who

Table 10.2 A set of results based on an oncology trial measuring patient-reported fatigue

Research question	Analytic approach	Results	Interpretation
Does the average change in fatigue symptom score improve more in the intervention arm compared to the comparator arm 3 months post intervention, regardless of disease progression?	A longitudinal analysis of group-level differences using an MMRM	The difference of LS means at visit 3 = −10.7 (SE = 2.06, 95% CI: (−14.7, −6.6)), $p \leq 0.0001$.	Higher post-baseline mean score of the intervention arm and the negative LS mean for the difference demonstrates a greater magnitude of improvement in the intervention arm compared to comparator arm, regardless of disease progression.
What is the difference in the proportion of patients still enrolled in the study at visit 3 in the intervention arm compared to the comparator arm who experience meaningful improvement in fatigue?	A responder analysis, supported by the CDF	Diff = 23.7% (95% CI = (8.6%, 38.8%))	48% of patients in the intervention arm experienced a meaningful level of improvement of at least 10 points on the fatigue measure, compared to 24% in the comparator after 3 months of treatment, for a difference of 23.7% (95% CI = (8.6%, 38.8%))
			The CDF (Fig. 10.3) demonstrates separation of the treatment arms across the continuum of change scores.
What is the likelihood of meaningful improvement of fatigue in the treatment arm versus the comparator arm over the course of 3 months of treatment?	GEE with MI	OR = 2.3 (95% CI: 1.3–4.2)	The odds of meaningful improvement for those in the treatment arm is 2.3 (95% CI: 1.3–4.2) times more than those in the comparator arm over the course of 3 months.

remained in the study at the third visit experienced a meaningful level of improvement on fatigue compared to 22% of those in the comparator arm. Lastly, over the course of treatment, patients in the intervention arm are 2.7 times more likely to experience a meaningful level of improvement on fatigue than those in the comparator arm.

10.10 Questions That Can Be Used for Learning/Testing

1. On PRO instruments, what items characteristics are important to understand prior to embarking on data analysis?
2. What are the main components of a PRO research objective?
3. Why are research objectives important?
4. What should be considered when analyzing multiple PRO endpoints?
5. What is a way to put multiple endpoints on a single, common, scale?
6. How is using a responder definition different from evaluating mean changes? What are the advantages/disadvantages?

10.11 A Topic for Discussion That Can Be Used in Teaching

There are multiple patient-reported instruments that can measure the same latent health-related quality of life concept. Further, results can report mean differences of groups, responder proportions, and odds ratios, to name a few. What are some of the challenges that occur when trying to understand the patient experience?

10.12 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

- Fairclough DL. Design and analysis of quality of life studies in clinical trials. CRC Press; 2010.
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10.13 Research in Context

An example of published PRO results from a clinical trial that demonstrated many of the best practices described in this chapter is given by Martin Stockler et al. (2015) in the *Journal of Clinical Oncology*. In the AURELIA trial, patients with platinum-resistant ovarian cancer were randomly assigned to chemotherapy alone (CT) or with bevacizumab (BEV-CT) [54]. HRQoL in patients with ovarian cancer was evaluated at baseline and every 2 or 3 weeks using the European Organisation for Research and Treatment of Cancer (EORTC), Core Quality of Life Questionnaire, the EORTC–Ovarian Cancer Module 28, and the Functional Assessment of Cancer Therapy–Ovarian Cancer symptom index. The second paragraph of the paper states the a priori PRO hypothesis that the add-on therapy of bevacizumab would lead to greater improvement of disease-related symptoms, especially in those who were symptomatic at baseline. Another statement "*The PRO hypotheses were not covered by the statistical testing strategy or sample size calculations for the main trial analysis, which focused on (progression-free survival)*" indicated that there was no controlling for multiplicity. Specifications of the analysis included the hypothesized direction of PRO change (improvement) and justification of the meaningful change threshold definition. The researchers assessed PRO compliance, specified the handling of missing PRO data, and articulated and conducted a number of sensitivity analyses of the primary responder analysis. Results were reported both in text and in several well-designed and annotated graphics: bar charts reported compliance and responder proportions; line graphs depicted the MMRM analysis of PRO change over time; and a forest plot summarized the differences in responder proportions, a standardized measure by nature, for the multiple subdomains within each instrument.

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11 Data Visualization Strategies to Communicate PRO Data to Patients and Clinicians

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11.1 Introduction

As has been addressed in detail in other chapters, patient-reported outcomes (PROs) can be utilized in clinical practice to promote patient-centered care in a number of ways. In this chapter, we refer to three broad "applications" of PRO data in clinical practice. The first of these is the use of PROs for patient monitoring and management [1, 2]. We refer to these PRO applications as occurring at the "individual patient" level, wherein a patient completes a PRO questionnaire and that particular patient's results are fed back to the clinician (and frequently also the patient) to help monitor the patient's progress and identify issues potentially requiring attention. The use of PROs for patient monitoring has consistently demonstrated benefits related to patient provider communication [3, 4]. It has also been shown to improve detection of problems [4, 5], affect patient management [6, 7], and improve patient outcomes, such as symptom control, health-related quality of life (HRQoL), and functioning [4, 8–10]. In some settings, randomized trials have also shown the use of PROs for patient monitoring to result in longer survival [10, 11].

Second, PROs can be used as outcomes in research studies. In these studies, PROs are calculated at the group level, and compared between intervention groups or within treatment group to address specific hypotheses or to describe patient outcomes. These published PRO results are used by clinicians to improve their understanding of treatment benefits and side effects, which informs their counseling of patients regarding treatment choices and thereby promotes patient-centered care [12–14]. Third, these same results from comparative research studies can be directly communicated to patients (e.g., in educational materials or formal decision aids) to inform patients about their condition as well as the benefits and risks of different treatment strategies. A systematic review of 86 studies of decision aids found evidence that they tended to improve knowledge and decrease decisional conflict compared to usual care, particularly when quantitative data were used in the aid [15].

Each of these three broad applications requires that PRO data from patients be communicated effectively, meaning that the data are accurately interpreted and are useful to clinicians and patients [16, 17]. However, visualizations of healthcare quality and risk data are often adopted based largely of common sense, or are driven by popular graphing software that may emphasize visually attractive (e.g., 3-dimensional) displays with marketing appeal over those that are optimally interpreted [18]. Information presentation has been examined in several research fields including psychology, market research, and information systems/management. Many of these studies have focused on aspects of presenting risks, such as the differential impact of risk perception with relative versus absolute risk, or by framing risks in the positive (e.g., increased chance of survival) versus the negative (increased chance of death) [19]. A further focus has been on examining verbal (e.g., "mild" or "rare") compared with numeric terms for risk [19]. Comparatively little research, however, has focused on strategies specifically addressing PRO data visualization. In this chapter, we examine the available literature and provide an interpretative summary of main principles arising from these studies.

This chapter will help readers appreciate why patients and clinicians may find PRO data visualization challenging, understand themes from the research literature regarding the optimal visual presentation of PROs to patients and clinicians, and learn about recently published evidence-based, stakeholder-driven recommendations for graphic display of both individual-level-patient and the group-level-research PRO data.

11.2 The Use of Graphs for Visualizing PRO Data

For PROs, the saying, "A picture is worth a thousand words," can be rephrased to "A picture is worth a thousand numbers" [20]. It makes sense, therefore, to consider pictures as an effective way of communicating PRO findings. The pictures used to communicate PRO data are typically graphs (but not always so, as will be discussed later). Graphs are used to make complex information visually salient. More formally, graphs can be defined as "a unique form of visuo-spatial depiction that represents quantitative information via an analogy between quantitative scales and visual or spatial dimensions, such as length, color, or area" [21].

Data visualization is the graphical display of quantitative information. Data visualization is commonly used for two purposes: making sense of the information (facilitating data analysis) and communicating the information effectively. As such, data visualization is a powerful means to discover and understand data that would otherwise be abstract, and to present this understanding to others [18]. Data have been displayed graphically for centuries, promoted initially principally by the French mathematician and philosopher Rene Descartes.

The successful translation of abstract data into physical attributes of vision (length, position, size, shape, area, and color, among others) depends on fundamentals of visual perception and cognition [18, 21]. A discussion of these fundamentals is beyond the scope of this chapter, but they can be briefly summarized by design principles that are derived from an understanding of human perception. Ware [22] provides a summary of these, concluding that successful data visualization must ensure that the design represents the quantities accurately, makes it easy to compare quantities, effectively illustrates the ranked order of values (where relevant), and indicates how the values relate to one another (i.e., part-to-whole relationship). Importantly, an effective data display should make obvious how people should use the information. Thus, graphs are an attractive way of depicting PROs, as they have the potential to make quantitative information easier to understand. Nonetheless, in some cases, the interpretation of graphs can be effortful and error-prone [21]. In the next section we review particular considerations for, and challenges of, PRO data visualization.

11.3 Challenges in Achieving Successful PRO Data Visualization

Successful visualization of PRO data presents a number of challenges, including the data constructs, users' familiarity with PROs, variation in present practice, and numeracy and graphic literacy.

11.3.1 The Variable Nature of PRO Data

Patient-reported outcomes are broad in design, purpose, and application. There are hundreds of different PRO questionnaires, and there are no standards for scoring or scaling across them. For example, on some PRO questionnaires, higher scores represent better outcomes (e.g., higher physical functioning), whereas on other PRO questionnaires, lower scores represent better outcomes (e.g., lower pain scores). On still other PRO questionnaires, whether higher or lower scores represent better outcomes depends on what is being measured (e.g., higher scores are better for functional outcomes but worse for symptoms). Beyond these inconsistencies in scoring directionality, there is also variation in

the scaling used. Some measures are scored 0–100 with the best and worst possible scores at each end of the scale, whereas other measures are normed to, for example, a general population average of 50. As a result of all of this variation, a score of "70" can have an entirely different meaning depending on the questionnaire used, its scoring convention, and how it is scaled.

11.3.2 Lack of Intuitive Understanding of PRO Scores

The variation in what PRO scores "mean," and how a score of 70 is interpreted, raises particular challenges for graphical displays of PRO findings. Many complex scores that we encounter on a day-to-day basis have some intuitive meaning. For example, although few people understand how a test of intelligence such as the Wechsler Adult Intelligence Scale (IQ) is scored and scaled, many people would recognize that a score of 140 is very high, or would recognize that a score of 120 represents higher intelligence compared to a score of 100. This inherent understanding likely results from repeated exposure to a measurement construct that is popularized without tremendous variation in its scoring metric. In contrast, both clinicians and patients have reported that variation in PRO scores confuses them and makes it challenging for them to use PROs in clinical practice. In studies examining use of individual patient PRO data for monitoring and management, a frequent complaint from patients and clinicians is that they do not know what the scores mean [23, 24]. Quotations from qualitative inquiry include "*Of course I have no idea if this is a good score or a bad score,"* and *"I got confused…trying to remember which ones had 100 as good and which had 100 as bad,"* and *"A score of say, 50, meant one thing on one graph and something different on another one, which I thought was strange"* [24]. For clinical trial results, a recent study found that fewer than half (42%) of oncologists felt comfortable interpreting PRO trial results, with many citing the variability in the data presented [14].

In a recent cross-sectional mixed-methods study, participants were asked to interpret two-line graphs, one with a line treading up (labeled "general well-being") and one with a line trending down (labeled "feeling short of breath," as illustrated in Fig. 11.1 [25]. While the context of the graph was explained in the study, the graphs were intentionally not labeled with cues for the directionality of scores. For the upward trending graph of "general well-being," 96% of the cancer patient participants ($n = 50$) interpreted the graph as showing improvement over time (2% indicated worsening and 2% were unsure). For clinician participants ($n = 20$), 80% interpreted the graph as improvement (5% worsening, 15% not sure). Qualitative comments supported an intuitive rationale that higher is typically better, such as *"…typically with graphs, as the line increases things are better…Especially like with money…when the line goes up everything is better."* Insofar as the downward trending line for "feeling short of breath," interpretations varied considerably. Of the cancer patients, 60% interpreted the trend as worsening over time, whereas 34% interpreted the patient to be improving and 6% were not sure. For the clinician participants, 70% felt the trend indicated improved symptoms, 10% worsening, and 20% were not sure. Qualitative comments revealed that some participants reasoned that a downward trend inherently reflected worsening, others felt that a downward trend reflected fewer symptoms (therefore feeling better) and still others were unwilling to guess: "*I don't know what's being scored and what are the values and what did those values mean.*" These findings emphasize the lack of reliable intuitive interpretation of PRO scores – particularly symptoms where lower scores may intuitively be seen as improvement (i.e., less symptom burden) or worsening (i.e., if higher is better, then lower must be worse). These challenges with consistent intuitive interpretation of PRO scores threaten their clear communication to both clinician and patient users.

11.3.3 The Variable Nature of PRO Data Reporting and Visual Presentation

Not only is there wide variation in PRO measures (and their scoring and scaling), and variation in the intuitive interpretation of PRO data, these data are

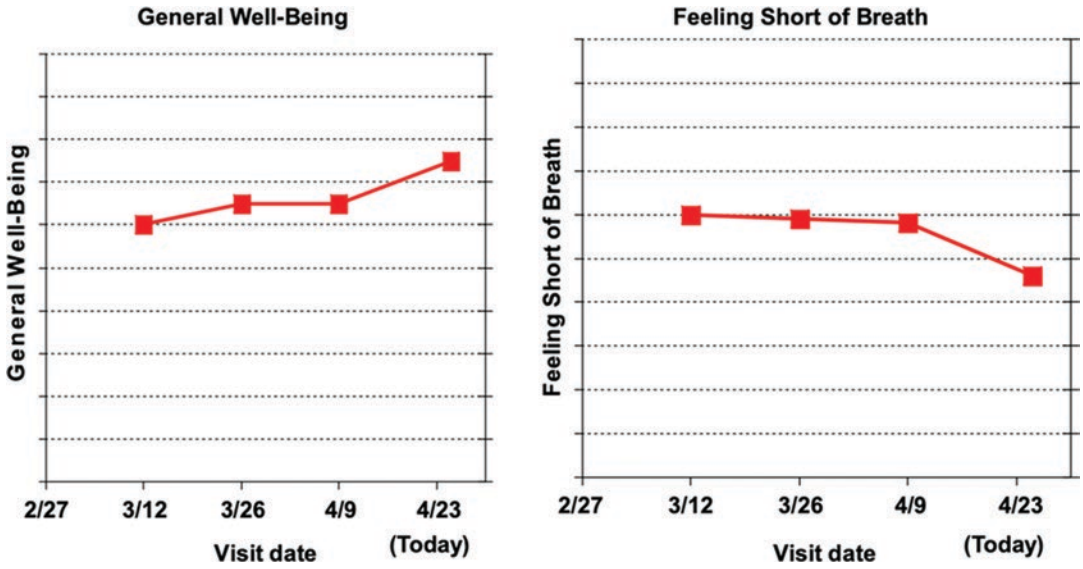

Fig. 11.1 Trend lines for PRO scores over time for two domain [25]. This figure was used to explore how study participants intuitively interpret upward and downward trends. (Reprinted by permission from Springer Nature: Brundage et al. [25], Copyright © 2015)

reported in a wide variety of graphic formats. Examples from the literature include the following: tabulations of the scores without graphs; line graphs of scores over time; bar charts of scores over time; "heat maps" showing background color shades as cues for better or worse scores; and bubble plots, radar charts, and other formats for displaying scores at a single time point. An additional layer of complexity in the group-level comparative effectiveness setting is the nature of the data summary used to report PROs. A systematic literature review of PRO clinical trial results found substantial variation in both in which summaries of data were used (mean scores, mean change scores, p-values only, responder proportions) and in how these data were presented (<1/3 of studies used graphs) [26]. This variability in data presentation adds further confusion regarding PRO interpretation.

11.3.4 Health Literacy, Graphic Literacy, and Numeracy

Finally, the inherent capacity of users to understand health-related issues, quantitative data, or illustrations of quantitative data is often limited, representing an additional set of challenges for communicating PRO data. A 2005 pooled analysis of health literacy rates in the United States, for example, estimated that the prevalence of low health literacy was 26% (95% CI: 22–29%), and a 2007 study estimated a prevalence of inadequate health literacy of 11% in a sample of British adults. With regard to numeracy, an estimated 30% of US adults lack sufficient numeracy skills to make calculations with whole numbers and percentages or to estimate numbers or quantities, and approximately 1 in 3 US adults have low graphic literacy. These findings suggest that some patients will require non-numeric or non-graphic strategies to understand PRO findings for patient-centered care.

11.4 Using Data Visualization to Improve PRO Communication: Emerging Themes from the Research Literature

Despite the above challenges to effective communication of PROs to clinicians and patients, it can be done successfully. The evidence that PROs in the individual patient setting can improve commu-

nication and care quality, and that PROs in research studies can be useful to patients and clinicians, implies that at least some PRO reports work well enough to achieve their desired effects. Specific studies of using graphs to communicate PRO findings have demonstrated that both patients and clinicians *can* interpret PRO data accurately, although some formats work better than others, as will be discussed below. While a great deal of research has explored how certain quantitative outcomes, such as risks associated with behaviors or interventions, can be effectively communicated, comparatively little research has been reported regarding effective data visualization for PROs specifically [19]. In 2016, Bantug and colleagues published an interpretive summary of the literature on graphic communication of PRO data. Below, we highlight themes arising from that literature, supplemented by more recent papers that address these topics.

Table 11.1 summarizes the key components of research papers that inform this interpretive summary. As can be seen, ten of these papers address the use of graphic display of PRO data in the individual-patient setting, and eight address the use of graphs for communicating group-level data summaries. A number of shared themes arise from this collective body of research. Rather than discussing each paper in detail, this section summarizes the common themes using illustrative examples.

11.4.1 Theme 1: Both Patients and Clinicians Can Interpret Some PRO Graphs Accurately

Across these studies, the literature shows that many patients and most clinicians can accurately interpret some graphical representations of PRO data. Virtually all studies that quantitatively assessed participants' understanding of displayed PRO data found one or more formats that the majority of patients and clinicians could interpret correctly. For example, McNair and colleagues conducted a semi-structured interview study in 132 cancer patients and found that 87% correctly interpreted the PRO data from two treatments when a single domain was presented (although accuracy dropped with more complex presentations) [27]. Brundage (2005) and colleagues [28] reported a multi-center study utilizing semi-structured patient interviews to evaluate how accurately patients interpreted group-level PRO information presented in six different formats and found that accuracy rates ranged from 85% to 98% across formats (line graphs of mean scores from a single PRO domain over time were interpreted most accurately). In contrast, Kuijpers [29] and colleagues reported a multi-center study of five data formats assessed by 775 patients and health professionals and found that 83% of patients rated the formats easy to understand, but objective understanding was only 59% among patients. Also, in the individual-patient setting, Izard [30] and colleagues conducted semi-structured interviews with patients and clinicians to test graph interpretation and found that comprehension for patients ranged from 79% to 89% across formats, whereas clinician comprehension ranged from 97% to 99%. In a large study of patients, clinicians, and researchers (n = 1113) interpreting six different formats for communicating individual-level PRO data, Snyder [31] and colleagues reported that accuracy of interpretation rates ranged from 53% to 100% across all participants and all accuracy outcomes. In a parallel study of 481 clinicians and researchers interpreting group-level PRO data presentation formats designed for research publications [32], accuracy rates ranged from 71% to 90% across formats showing mean scores over time, and ranged from 85% to 98% for formats showing proportions of subjects with worsened, stable, and improved PRO scores. Thus simple formats, such as line graphs, over time seem to be consistently accurately interpreted, although studies reveal mixed findings regrading other format styles.

11.4.2 Theme 2: Participants' Most Preferred Formats May or May Not Be the Most Accurately Interpreted Formats

Several studies illustrate that objective assessments of participants' accuracy in interpreting PRO data displays may differ from their format preferences or their subjective ease-of-

Table 11.1 Evidence focused on graphic presentation of patient-reported outcome data to patients or clinicians

Author, year	Population	Setting	Data collection	Patients or clinicians (*N*)	Level of PRO data	Main findings regarding PRO graphs
Detmar, 2002 [4]	Variety of adult cancers	Ambulatory cancer palliative chemotherapy	Randomized crossover trial where patients completed a HRQOL questionnaire	Patients (214)	Individual	Patient PRO responses were compiled into a graphic summary and given to the patient and provider prior to the consult encounter (patients did not evaluate the graphic profiles themselves)
				Clinicians (10)		
			Assessment of a graphic PRO summary was a secondary outcome			Physicians reported that the summary profile provided a useful overall impression of their patients' symptom experience
						The graphic profile facilitated communication
						Enhancements to the graphic format were suggested by some physicians
Berry, 2004 [33]	Variety of adult cancers	Radiation therapy ambulatory care	Focus groups informing interface design (for use in an intervention assessment study)	Clinicians (6)	Individual	Focus group recommendations included clinician priorities of brevity, flexibility, and simplicity for both input interface and output
						The assessment output should contain color graphic displays
						Graphs with flagged areas of concern should be made available to providers
Snyder, 2009 [23]	Variety of adult cancers	Outpatient oncology practice	Interviews informing interface design (a prototype website to collect PRO data and link it with the electronic medical record)	Patients (20)	Individual	Clinicians reported that the website could be most helpful in tracking symptoms over time and could improve clinical practice if the process was not too burdensome
				Clinicians (7)		
						Patients felt the website could facilitate communication with their clinicians
Izard 2014 [30]	Prostate cancer	Outpatient prostate-cancer practice	Interviews and quantitative assessments (participants assessed graphic arrays of prostate cancer PROs derived from patient focus groups)	Patients (50)	Individual	Comprehension and preferences were scored for table, bar, line, and pictograph formats
				Clinicians (50)		For patients: overall accuracy ranged from 79% (pictographs) to 88% (line and bar graphs); reading accuracy was 92% for line and bar graphs.
						For clinicians: accuracy was high for all formats (97–99%)
						Patients and providers preferred bar charts to other formats

(continued)

Table 11.1 (continued)

Author, year	Population	Setting	Data collection	Patients or clinicians (*N*)	Level of PRO data	Main findings regarding PRO graphs
Kuijpers 2015 [47]	Variety of adult cancers	Hypothetical reports of individual PRO scores	Questionnaire assessing objective and self-rated understating, and preferences, for five data presentation styles	Patients (548)	Individual	Patients (83%) and clinicians (85%) rated formats as easy to understand (no differences between styles)
				Clinicians (227)		Objective understanding was 59% (mean correct responses) in patients and 78% in medical specialists; no differences were seen between formats
						Patients preferred colored bar charts, whereas clinicians preferred colored heat maps
Snyder 2017 [31]	Variety of adult cancers	Hypothetical reports of individual PRO scores	Mixed-methods study using e-questionnaire and qualitative data (open-ended responses and 20 patient and clinician interviews)	Patients (627)	Individual	Accuracy of interpretation rates ranged from 53% to 100%
				Clinicians (236)		Formats with consistent directionality (higher scores always indicating better health status) more accurately interpreted (OR 1.30) and more likely to be rated as "very clear" (OR 1.36) than those with mixed directionality
				Researchers (250)		Threshold-line formats indicating concerning scores were more likely to be rated "very clear" than were red-colored data points (OR 1.22) or background shading formats (1.43)
Stonbraker 2020 [37]	Persons living with HIV	Subjects recruited from the community	Phase 1 qualitative development; phase 2 evaluations	Persons living with HIV (55)	Individual	94% preferred formats with emojis; most popular format was bar graphs annotated with emojis
						End-users provided suggestions for further improvements
Turchioe 2020 [41]	Cardiac patients	Hospitalized with heart failure	Structured interviews with randomized presentation order for four data formats	In-patients (40)	Individual	Formats with visual analogy (e.g., gas gauge) were most often comprehended (83%) compared to line graph (60%) or text only (63%)
						Of participants who comprehended at least 1 condition, 14% preferred a condition that they did not comprehend
						Low comprehension was associated with worse cognition, lower education level, and fewer financial resources

Author, year	Population	Setting	Data collection	Patients or clinicians (*N*)	Level of PRO data	Main findings regarding PRO graphs
Engelen 2010 [48]	Children	Pediatric oncology practice	Focus group informing interface design	Clinicians (6)	Individual and group levels	A descriptive paper highlighting the development, implementation, study design, and outcome measures of a PRO on HRQOL in clinical practice
Brundage 2015 [25]	Variety of adult cancers	Hypothetical scenarios	Mixed methods including purposefully sampled participants, a self-directed exercise, and qualitative interviews	Patients (50)	Individual and group levels	Six group-level data formats and four individual level formats were included
				Clinicians (20)		For group-level formats, line graphs of scores over time were rated highest by patients for ease of understanding and usefulness. Clinicians rated simple line graphs as easiest to understand, but preferred line graphs with confidence limits or normed scores
						For individual-level formats, both patients and clinicians rated line graphs highest for ease of understanding and usefulness. Qualitative data supported highlighting scores of possible clinical concern and providing reference values
Brundage, 2003 [49]	Variety of adult cancers	Hypothetical scenarios	Focus groups exploring preferences (among 10 written and visual PRO presentations)	Patients (35)	Group	Simple formats preferred to more complex graphics, regardless of educational level
						Line graphs of average scores rated highest overall in both high- and low-education groups
						Individuals varied as to their most preferred format
Brundage, 2005 [28]	Variety of adult cancers	Hypothetical scenarios	Interviews and quantitative assessments	Patients (198)	Group	Across six PRO presentation formats, accuracy ranged from 85% to 98% of patients
						Line graphs of average scores over time were the most accurately interpreted (98%) irrespective of age or education level
						Age and education level were independently predictive of accuracy across formats
McNair, 2010 [27]	Esophageal or gastric cancer	Hypothetical scenarios	Interviews and quantitative assessments	Patients (132)	Group	87% of patients understood both line graphs of single domain PROs
						67%–82% of patients understood each of three questions about integrating two graphs
						Higher education and younger age were significant predictors of understanding (univariate only)

(continued)

Table 11.1 (continued)

Author, year	Population	Setting	Data collection	Patients or clinicians (*N*)	Level of PRO data	Main findings regarding PRO graphs
Cocks 2014 [38]	Breast cancer	Hypothetical scenarios	Interviews assessing outcome interpretation	Patients (11)	Group	Patients were assessed on their ability to use published data to judge the size of differences in QOL scores; their ability to understand a questionnaire in an interview format; and their ability to understand the difference between group level and individual data
						Opinions on differences in QOL scores varied and were often based on their own experiences of cancer and its treatments
Tolbert 2019 [35]	Variety of adult cancers	Hypothetical PRO reports designed for patient direct use	e-Questionnaire (and 15 additional qualitative interviews). Accuracy rates and clarity ratings assessed in multivariate analyses	Patients (629)	Group (proportion changed)	Bar charts less accurately interpreted than pie charts (OR 0.39) and icon arrays (OR 0.47)
				Clinicians (139)		
				Researchers (249)		Bar graphs and icon arrays were less likely than pie charts to be rated "clear" (OR 0.37 and OR 0.18)
						Patients, clinicians, and researchers all interpreted pie charts more accurately than the other formats
Tolbert 2018 [36]					Group (over time)	Line graphs with consistent directionality (higher scores always indicate better health status) were more accurately interpreted than those with mixed directionality, either using absolute scores (OR = 1.43) or normed scores (OR = 1.88)
						Line graphs with consistent directionality were more likely to be rated as "clear" than those with mixed directionality (OR = 1.51)
						Patients were less likely to interpret line graphs accurately compared to researchers (OR = 0.62), whereas no difference was found between clinicians and researchers
Brundage 2018 [32]	Variety of adult cancers	Hypothetical PRO reports of group scores designed for research publications	e-Questionnaire (and 10 additional qualitative interviews). Accuracy rates and clarity ratings assessed in multivariate analyses	Clinicians (233)	Group (proportion changed)	Accuracy rates (no incorrect answers on two test questions) ranged from 85% to 98% across participant groups and format types
				Researchers (248)		
						Respondents were less likely to make an interpretation error with pie versus bar charts (OR 0.35); clarity ratings did not differ between formats

Author, year	Population	Setting	Data collection	Patients or clinicians (*N*)	Level of PRO data	Main findings regarding PRO graphs
					Group (over time)	Accuracy rates (no incorrect answers on two test questions) ranged from 71% to 90% across participant groups and format types
						Line graphs with consistent directionality (higher scores always indicate better health status) were more likely to be interpreted accurately than normed line graphs with mixed directionality (OR 1.55)
						Graphs with consistent directionality were also more likely to be rated "very clear" compared to normed data (OR 1.91)

interpretation ratings. In the study by Izard reporting patients' interpretation of individual-level data, patients' preferences for different formats varied much more than did comprehension rates. However, pictographs of QOL status (using happy face emojis) were both the least preferred and the least accurately interpreted [30]. Brundage (2005) reported that the graph format most preferred by patients – line graphs over time – was also the format most accurately interpreted by patients. However, some other formats with high preference scores were less accurately interpreted [28]. In large e-survey of clinicians (n = 233) and researchers (n = 245) interpreting group-level PRO data display formats [32], participants were significantly less likely to make interpretation errors with plain line graphs versus normed line graphs (even when both used mixed directionality); participants were also significantly more likely to rate the plain line graphs as "very clear." In contrast, in the same study, participants were significantly more likely to make errors interpreting bar charts of proportions changed compared to pie charts, though the clarity ratings were not significantly different [32]. The most striking discord between subjective and objective understanding was seen in the Kuijpers study where 83% of patients found the formats easy or very easy to understand, yet were accurate on average only on 59% of assessments [29].

11.4.3 Theme 3: The "Target Audience" Is an Important Consideration in the Data Presentation Strategy

PRO data strategies can vary in complexity in a number of ways, and this complexity can influence interpretation accuracy and perceived usefulness of the strategy [33]. Simple formats include a line graph showing mean scores over time, or in the case of proportions, a pie chart. Common additional complexities include using less familiar scaling strategies (e.g., normed data), displaying more than one PRO domain at a time (particularly if the directionality of improvement differs between domains), adding annotations (e.g., confidence limits or p-values), or displaying more cognitively challenging outcomes such as mean change scores or a cumulative distribution of proportions changed by a continuum of cut points. Studies that have examined presentation complexity and accuracy of interpretation have typically found an inverse relationship. In the Brundage (2005), McNair, and Izard studies, accuracy of interpretation dropped with either more dimensions shown simultaneously or more complexity added in a single presentation format [27, 28, 30].

A three-part mixed-methods study addressed the association between data format and understanding among patients, clinicians, and PRO researchers [25, 31, 32, 34–36]. Qualitative inquiry revealed that across six presentation strategies, plain line graphs were typically felt to be straightforward and clear for both patients and clinicians [25]. Line graphs of scores normed to an average score of 50 appealed to some clinicians who liked the scoring metric, whereas patients typically felt normalized scores to be too "convoluted" and lacked confidence interpreting them. Line graphs that included confidence limits appealed to many clinicians, but patients typically did not know what the confidence limits were, were confused by them, or did not feel they added anything. Bar charts illustrating the proportion of patients that were stable/worsened/improved appealed to some patients and clinicians, but many found that the single cut point (used to define change) and the single point in time were not as helpful as trends over time shown by line graphs. A more complex cumulative distribution of proportions changed over a continuum of cut points was typically felt to be unfamiliar, non-intuitive, and thus difficult to understand. When patients rated the ease of understanding and perceived usefulness of these formats, simple line graphs were rated highest in both dimensions. When asked to choose which of the six formats was most useful, line graphs were most commonly selected (33%), and bar charts showing proportions changed were selected by 20%. When clinicians rated the perceived clarity of each format, simple line graphs scored highest.

When asked to pick which format, they would prefer to use, however, line graphs with confidence limits (30%) and normed line graphs with confidence limits (30%) were most often selected. These findings indicate that there is no one format that is clearly superior across participants. It is also clear that clinicians have different preferences than patients. Both prefer simple formats, but clinicians tend to value additional information such as confidence limits or normed scores. Visualization strategies need to accommodate these differences in user needs.

Insofar as patient sub-groups are concerned, some studies that have examined the association between education and accuracy of PRO graph interpretation have shown mixed results. Brundage et al. found little difference in format preference between high and low education groups, using both qualitative and quantitative measures [28]. Patients with more education were better able to interpret complex PRO data (e.g., proportions of patients improved) accurately, but simple line graphs of average scores were more accurately interpreted than complex formats regardless of education level. McNair et al. found only weak evidence that more education increased understanding, reporting that most patients understand graphical multidimensional PROs [27]. In terms of age, Brundage found that patients >65 years were less likely to interpret PRO graphs correctly [28], while the study of McNair et al. found a statistically insignificant decrease in the odds of understanding graphs with age [27]. Notably, although some of these studies purposefully sampled patients of different education levels, age, and/or gender, formal assessments of patients' health literacy or graphic literacy were rarely included. Stonbraker and colleagues [37] specifically explored graphic formats for PRO communication in a population with low health literacy and found that a bar graph combined with emojis was participants' preferred format and the one that promoted comprehension. They further pointed out that including end-users in design was helpful in identifying how subjects interpreted images and to ensure final products were meaningful. Finally, few studies have explored explanations for why subjects misinterpret graphic PRO data, although Cocks [38] found that some cancer patients "substituted" their own experiences when trying to evaluate the magnitude of quality of life scores provided by other patients. Qualitative findings from the three-part mixed-methods studies revealed that some errors are related to format characteristics (e.g., confusion resulting from mixed directionality in a single display, or sub-optimal use of figure legends) [25, 31, 32, 34]. Other errors related to individual characteristics, such as self-disclosed lack of graphic literacy or, in the case of clinicians, lack of understanding of statistical concepts such as *p*-values and confidence limits.

11.4.4 Theme 4: Consistent PRO Score Directionality Can Impact Accuracy of Interpretation and Perceived Usefulness

As mentioned above, PRO score directionality can vary both between and within some PRO measures, and there is no clear intuitive interpretation of directionality for many symptom scores. The parallel studies reported by Snyder [31], Brundage [32], and Tolbert [36] report findings specifically exploring these issues in the individual-patient setting and in the comparative group setting, respectively. In these studies, participants saw line graphs over time for four domains (two function scales and two symptom scales, see Figs. 11.2, 11.3 and 11.4). Participants were randomized to see these domains with higher scores always "better," with mixed directionality (higher scores better for function but worse for symptoms [i.e., greater symptom burden]), or with normed scores (also with mixed directionality, example not shown). For the study in which participating patients viewed individual-level data, the formats using consistent directionality (higher = better across domains) were significantly more accurately interpreted than formats with mixed directionality (illustrated in Fig. 11.2). For participating patients viewing group-level data, the accuracy rates were again statistically significantly superior for the format using consistent directional-

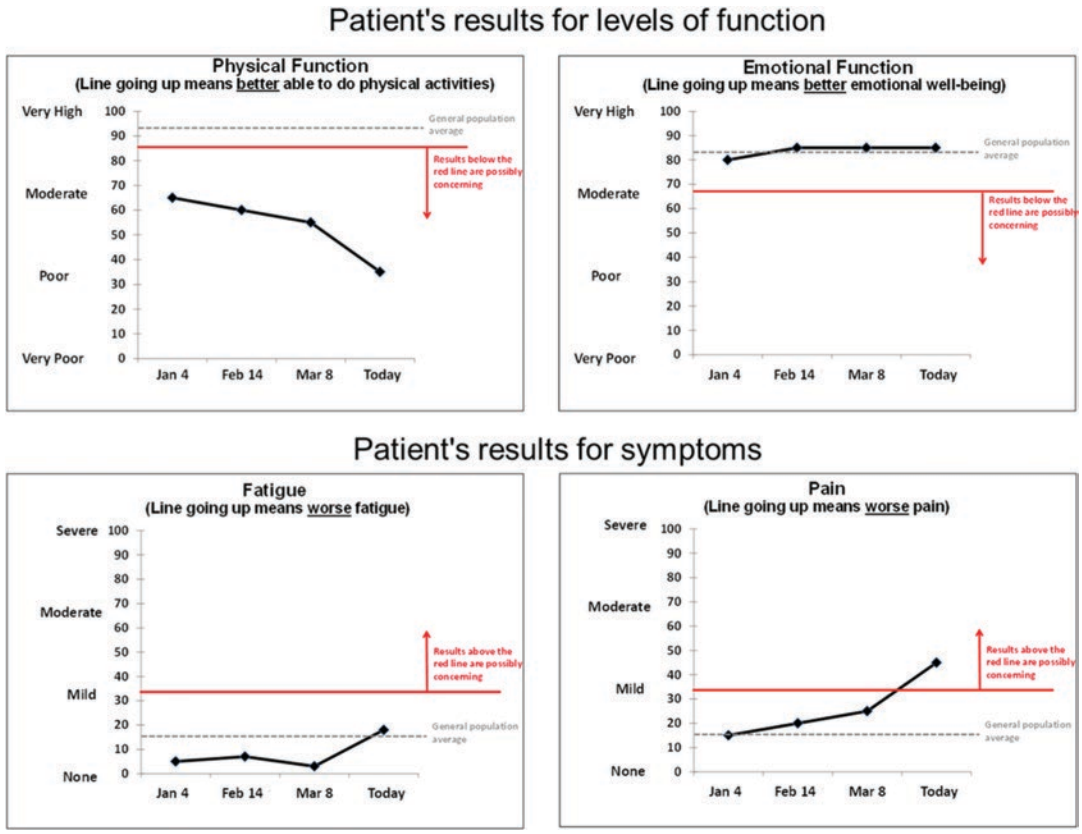

Fig. 11.2 Format recommendations for presenting individual-patient-level PROs to patients and clinicians [20]. (Reprinted by permission from Springer Nature: Snyder et al. [20], Copyright © 2019)

ity (higher = better across domains), both when compared to the mixed direction "more" format (illustrated in Fig. 11.3) and the "normed" format. The consistent directionality format was also more likely to be rated as clear compared to the mixed direction format. For clinician participants, there were no statistically significant differences in the odds of accurate interpretation between the "more" and "better" formats, and clarity ratings also were not significantly different between the two. Both the "more" and "better" formats, however, were more accurately interpreted and more likely to be rated as clear compared to the normed format. These findings indicate that the variation in directionality between domains is not only subject to different intuitive interpretations but can also negatively impact on the accuracy of interpretation when combined in a visual display across domains.

11.4.5 Theme 5: Clinicians' Abilities to Interpret p-Values, Statistical Significance, and Clinical Significance on Graphs Vary

Evidence suggests that clinicians and researchers have varying levels of ability to accurately interpret statistical annotations, such as confidence limits and p-values. In the three-part mixed-methods studies, for example, clinicians were asked to interpret the statistical significance of a displayed difference in mean PRO point estimates at a single point in time (displayed as part of a line graph of mean scores over time with confidence limits illustrated at each time point) [32]. Qualitative findings showed that some clinicians understood the use of confidence limits, whereas others inappropriately cited the overall

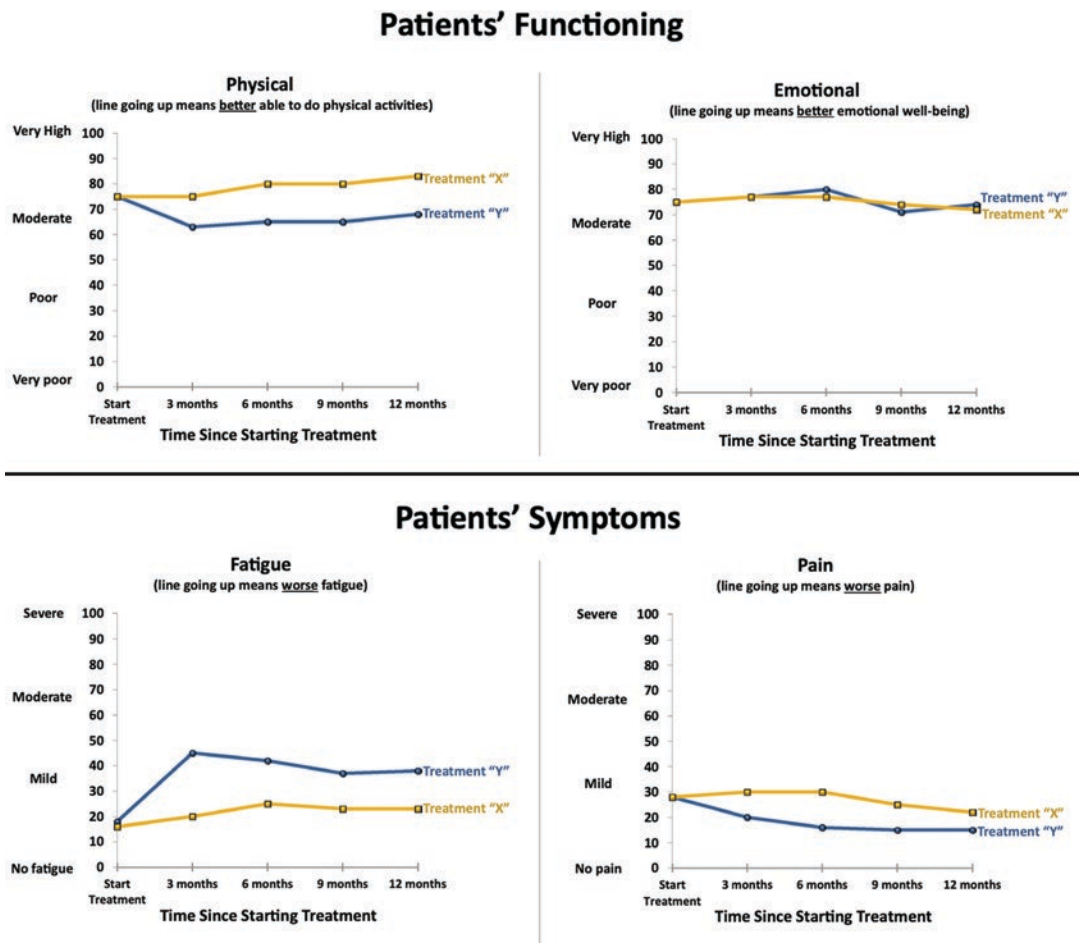

Fig. 11.3 Format recommendations for presenting group-level mean PRO scores over time to patients [20]. (Reprinted by permission from Springer Nature: Snyder et al. [20], Copyright © 2019)

trend p-value, and others admitted to being unsure how to interpret the graph. While some participants valued the information provided by confidence limits, other felt that they only added complexity. Quantitative findings in the e-survey of clinicians [32] showed that 80% of respondents recognized that two means with widely separated (non-overlapping) confidence limits were statistically significantly different (whereas 20% did not) and 12% rated two means as statistically different even though the confidence limits were nearly completely overlapping. As statistical recommendations for comparing mean scores move toward emphasizing the use of confidence limits over p-values, some clinicians may require guidance to increase their familiarity and understanding of these illustrations in practice.

Evidence also suggests that the concept of clinical significance is difficult for some clinicians to interpret, even with legends and annotations. In the e-survey of clinicians, fewer than half of clinicians surveyed (44%) could accurately report clinically significant differences between groups at a given time point, even though those differences were clearly described as at least 10 points between mean scores estimates, and were additionally marked with an asterisk at relevant time points [32]. Qualitative findings revealed that some clinicians reported being unfamiliar with the concept of clinical sig-

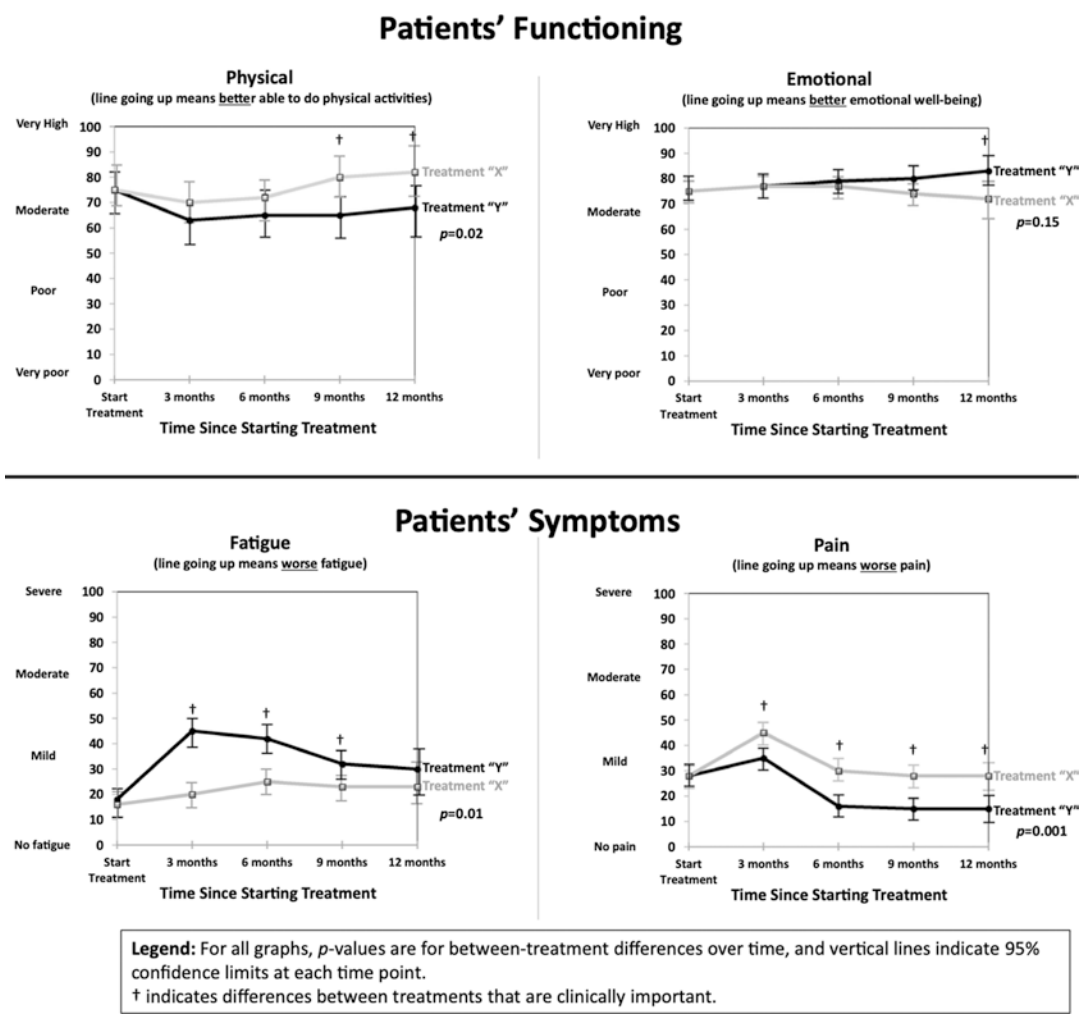

Fig. 11.4 Format recommendations for presenting group-level mean PRO scores over time to clinicians and researchers [20]. (Reprinted by permission from Springer Nature: Snyder et al. [20], Copyright © 2019)

nificance, some felt that the magnitude of difference in mean scores was hard to see, and some entirely missed the legend with the annotations explained.

11.4.6 Theme 6: The Visual Display Should Be Appropriate for the PRO Objective(s) of the Study

As noted earlier, PRO measures are used in a variety of research-related applications. For these applications, there is no "one size fits all," and the visual display of the data should be consistent with the underlying PRO endpoint addressing the objective of the measurement strategy.

In research applications using group PRO findings, a common data summary is a report of group mean (change) scores over time, addressing either between-group or within-group study objectives. For these reports, line graphs displaying mean (change) scores over time are appropriate. Some studies address the objective of describing the proportions of participants improved, unchanged, or worsened (according to a cut point defining meaningful change) at a certain time from baseline. That is, an intervention

that results in a much higher proportion of patients improved with respect to a particular PRO domain may have clinical value, and this strategy may be an effective way of summarizing PRO findings for both patients and clinicians. The study by Tolbert and colleagues [35] reported an e-survey of cancer patients, clinicians, and researchers who viewed three graphic representations of proportions changed (pie charts, bar charts, and icon arrays) designed for patient-facing applications such as educational materials. Figure 11.5 illustrates two of these variations, presenting the same research results in each format. As summarized in Table 11.1, multivariable analysis showed that bar charts were the least accurately interpreted and that pie charts were most likely to be rated as clear and interpreted most accurately. Although pie chart formats are often critiqued owing to the fact that accuracy of interpretation depends on correct perception of the angle and area of each slice, this limitation was overcome by labeling the proportions directly with annotations, and limiting the number of categories to three. Also as shown in Table 11.1, the parallel study of formats for displaying the proportions changed for clinician-facing applications also showed that clinicians and researchers are less likely to make interpretation errors with pie charts compared to bar charts, although clarity ratings were similar for the two formats. In sum, under the study circumstances, pie charts were rated as clearest, were most accurately interpreted, and were frequently appreciated qualitatively for their simplicity and ease of interpretation.

Some PRO measures are emerging that use categorical data, rather than the continuous data scales reported by the abovementioned formats. A measurement strategy used increasingly in oncology is the PRO-CTCAE, an item library designed to improve detection of adverse events by complementing clinician-rated toxicity grades for cancer therapies with corresponding patient-rated categories across a number of subjective symptoms [39]. For each adverse event, up to three individual items are administered to patients to evaluate frequency, severity, and interference with daily activities. Each item is scored by category (e.g., "mild" or "moderate" for severity and "a little bit" for interference). The objective of these data is to describe the proportions of patients in each category, and the data thus lend themselves to stacked bar charts showing the frequency of each score in each category for a given item, with the overall height indicating any adverse event. A simplifying algorithm for combining attributes into a single composite grade category has also been validated and is displayed similarly [40].

Finally, some measures employed to evaluate quality of life are non-numeric, such as "happy faces" of varying characteristics to indicate pain experiences or other types of emojis to reflect dimensions of well-being [37, 41]. In the Stonbraker study [37] of PROs for individual patients, many with limited health literacy, the objective was to communicate PRO scores with limited use of numerical data. This study found that "face emojis" combined with bar charts was the format preferred by 94% of subjects, and this approach also promoted comprehension. Similarly, Turchioe and colleagues [41] studied four formats for communicating PROs to cardiac patients and found that visual analogies (e.g., using a gas-gauge analogy to represent physical function) combined with a scaled score was the most accurately interpreted format.

11.4.7 Theme 7: Making PRO Scores Meaningful

Common to many of the above themes are issues underpinning the accurate interpretation of PRO displays. Beyond simply "getting the correct answer," adding "meaning" to the PRO scores may require additional strategies.

For the application of PROs in routine clinical care, a recent supplement in *Medical Care* reported a series of peer-reviewed papers designed to be used as a "tool kit" focused on two themes: helping patients and clinicians interpret PRO scores in the individual patient care setting and to act on patients' reports [17]. While the implementation issues (e.g., interface with the medical record or acting on alerts) are beyond the

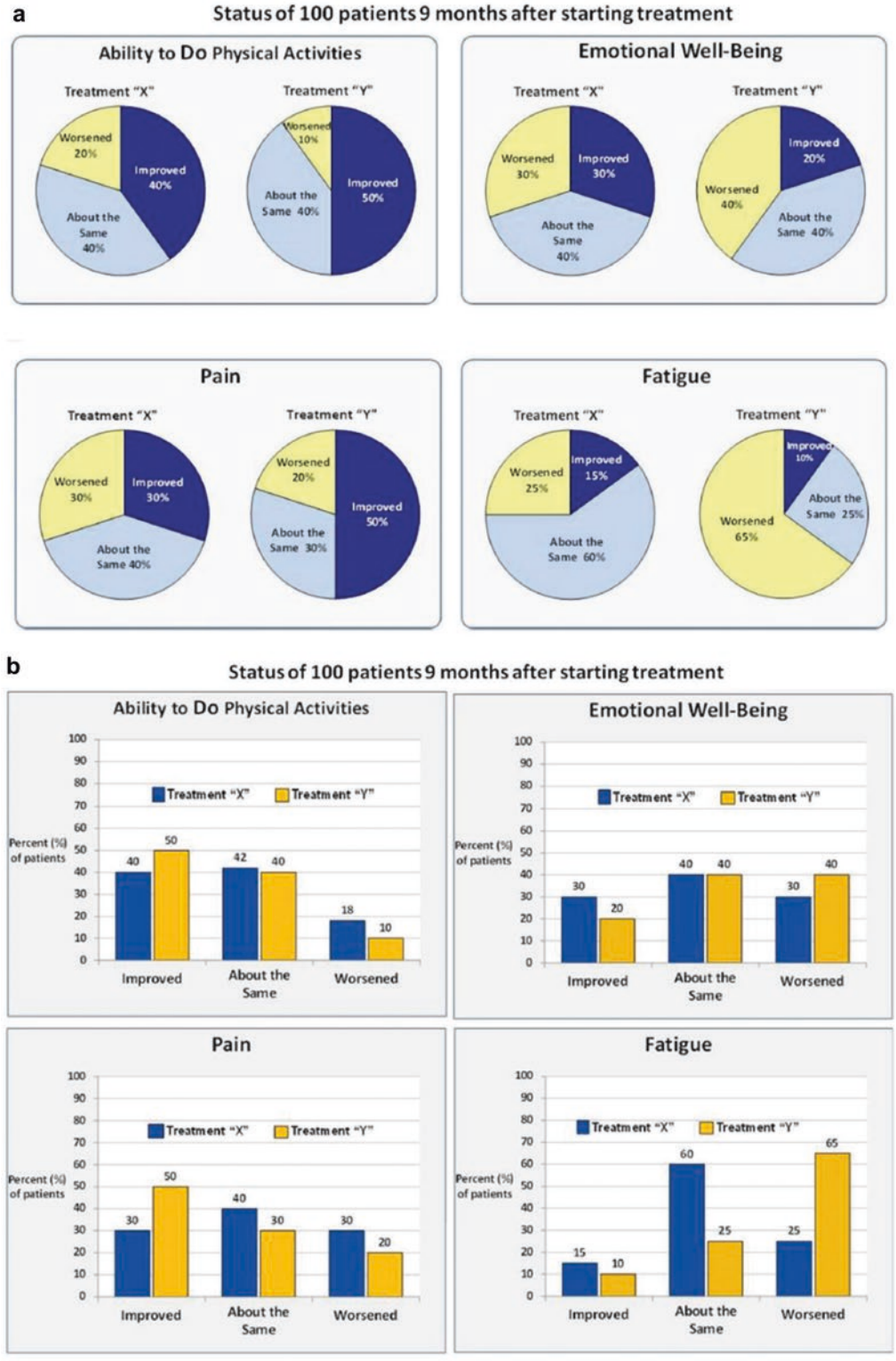

Fig. 11.5 Two examples of formats ((**a**) pie charts and (**b**) bar graphs) used to determine interpretation accuracy and perceived clarity of patient-reported outcomes (PROs) when providing proportions-changed data to patients [34]. (Reprinted by permission from Springer Nature: Tolbert et al. [35], Copyright © 2019)

scope of this chapter, four papers offered insight as to how to improve the interpretability of PRO scores (e.g., the horizontal lines in Fig. 11.2 illustrating potentially concerning scores and general population averages respectively). Two of these papers addressed ways to develop "cut points" on the graphical score axis to provide meaning: Shi and colleagues [42] addressed statistical methods for determining actionable cut points, and Cook and colleagues [43] reviewed the qualitative approach of 'bookmarking' to determine scale cut points. Both strategies aimed to link descriptors such as "mild" or "moderate" to scores reported by patients. Further, Browne and Cano [44] discussed how leveraging psychometric rating scales could aid the interpretability of scores over time, and Jensen and Bjorner [45] built on the concept of clinical "reference values" that clinicians routinely use to interpret laboratory data. Each of these strategies has the potential to be incorporated into visual displays of individuals' PRO data.

In group-level data applications, similar strategies for determining scale cut points can inform placement of axis labels (e.g., Figs. 11.3 and 11.4) that can aid interpretability of the scores. In addition, King and colleagues [46] reviewed the concept of clinically meaningful differences as applied to both the group and individual-patient settings; in group-level applications, the between-group scores that are considered clinically important can be explicitly illustrated, as shown in Fig. 11.4. Finally, scores for reference populations can also be employed in the group setting if relevant and normed scores may also explicitly indicate the norm value visually to aid in its interpretation.

11.5 Putting the Research into Context

The above sections highlight the many challenges and summarize key evidence that informs how to improve the communication of PROs in all three clinical applications. In addition to finding accurate and user-friendly ways of communicating PRO data, an important mission for the PRO research community is to promote consistency of PRO visual presentations to increase users' familiarity with the data summary strategies. Consistency of data presentation has been successful, for example, in promoting the understanding of actuarial estimates of survival times using Kaplan-Meier plots, or illustrating odds ratios across randomized trials included in a meta-analysis using forest plots. These are complex calculations and statistical comparisons, but the consistency of data display strategies promotes familiarity and understanding.

With the guiding principle of developing a consistent PRO data display platform, Snyder and colleagues undertook an international modified-Delphi consensus development project to develop stakeholder-driven and evidence-based recommendations for the display of PRO data in all three clinical applications [20]. The focus was on studies in oncology settings and purposefully included key stakeholder groups: cancer patients/caregivers, oncology clinicians, PRO researchers, and stakeholders specific to particular applications (e.g., electronic health record vendors, decision aid experts, and journal editors for each application, respectively). Key guidelines that informed the recommendations were that the displays should work on paper, should be interpretable in gray scale, could be enhanced with – but not dependent on – electronic presentation, and should be as simple and intuitively interpretable as possible. Specific recommended standards for the visual presentations of PROs for each of the applications are reported elsewhere [20] and illustrated visually in Figs. 11.2, 11.3, and 11.4. In the following, we briefly summarize the key recommendations.

Issues related to score directionality and conveying score meaning were common to all three PRO applications. With regard to score directionality, recommendations recognized that no single interpretation of score directionality was correct, and strategies to make directionality clear should be used, including using exceptionally clear labeling, titling, and other annotations where relevant, and warned against mixing score direction in a single display (i.e., a single figure). Whereas the consensus panel advised against any change

in how PRO scores are displayed to make the direction consistent, a rare exception was considered possible in journal publications where changing the directionality of display for consistency would be appropriate (e.g., when only one of many domains is scored in the opposite direction) but also that this reversal should be made transparent.

With regard to conveying score meaning, recommendations included that descriptive labels (e.g., none/mild/moderate/severe) along the y-axis are helpful and should be used when data exist to support their placement on the scale, particularly for the extreme categories (e.g., none, severe) that can generally be placed at the lowest and highest scale scores (Figs. 11.2, 11.3 and 11.4). For applications using patient-facing displays, recommendations included the display of reference values for comparison populations, when available (Fig. 11.2). For clinician-facing presentations, the Consensus Panel recommended the inclusion of the reference values simply be considered for inclusion.

Figure 11.2 illustrates additional recommendations for individual-patient applications. Some indication of possibly concerning scores in absolute terms was recommended (where evidence exists to support the concerning PRO score range), and it was also noted that more evidence was needed to inform the optimal approach for displaying possibly concerning changes in scores. The Panel recommended including some indication of possibly concerning scores (in this example, a directional threshold line) and suggested possibly using the same approach for the PRO scores as other data in the local electronic medical record.

Figures 11.3 and 11.4 illustrate the recommendations for displaying PRO research results to patients and to clinicians, respectively. There was consensus that displays should accommodate both normed (not shown) and non-normed scoring. Displaying the norm was considered optional, given the added complexity, but when the norm is shown, the reference population should be labeled clearly. It was also noted that information about the norm may be less relevant in the context where the focus is on the comparison between treatment options, and that for patients, it may be necessary to explain that the reference population may not be applicable to a given patient. Further research was recommended regarding optimal ways of displaying normed data and illustrating possibly concerning changes in scores for patient-facing materials.

Figure 11.4 also illustrates strategies for including information on statistical and clinical significance for publishing PRO research findings. The Consensus Panel recognized that clinicians appreciate p-values, but also that the trend in statistical approaches is moving away from reporting p-values to reporting confidence intervals. It was recommended that confidence intervals always be displayed, regardless of whether p-values are reported. As shown in Fig. 11.4, confidence limits can be used for individual time points, with p-values for the overall difference between treatments over time. The Panel further recommended indicating clinically important differences in journal publications using some sort of symbol (described in a legend), but not an asterisk due to its association with statistical significance. They also advised reporting in the legend and/or in the text of the paper when the clinically meaningful difference for a PRO measure is unknown.

For reporting proportions of participants meeting a responder definition to patients, the Panel recommended use of pie charts with slice labels (Fig. 11.5), given the evidence base supporting this format in patient respondents. For publishing PRO findings, the evidence base was not as conclusive, and therefore no single format was recommended; pie charts, bar charts, and stacked bar charts were all seen as reasonable approaches.

11.6 Moving Forward

The stakeholder-driven, evidence-based consensus recommendations are a clear step forward to promoting consistent strategies for displaying PRO data. A current challenge is to disseminate and implement these recommendations, a challenge that has been taken on by the PROTEUS Consortium (PRO Tools – Engaging Users and

Stakeholders). PROTEUS is an international consortium that aims to optimize the use of PROs in clinical trials and clinical practice by implementing and disseminating these recommendations for PRO data visualization and other relevant guidance documents. The PROTEUS website (www.TheProteusConsortium.org) provides helpful resources, including a repository of key references, checklists for applying recommendations, and video tutorials addressing visualization and other aspects of PRO use in research and practice.

With advances in technology both for collecting PROs (e.g., enhanced e-PRO reporting) and reporting PROs (e.g., customizable reports and new graphic interfaces), the field of data visualization for PROs will no doubt quickly evolve. The recently formed SISAQOL-IMI group is undertaking an expanded series of work packages, including one focused on further improvements to PRO visualization standards, including an updated systematic literature review and consensus-building efforts.

While the evidence base supporting new developments grows, additional research is clearly required to further the field of PRO visualization and communication. Specific areas for future research identified by the Delphi Consensus project included, among others [20], the investigation of new approaches to address the inherent confusion associated with inconsistency in directionality across instruments, to develop future PRO measures with consistent directionality, to continue to identify specific score ranges with clinically meaningful differences (and to improve the descriptive labels for these beyond "mild" and "moderate" for example), and finding optimal ways to communicate complex PRO concepts (e.g., minimally important change/differences, normed data, and reference populations), particularly to patient users.

11.7 Summary

Although PRO data have enormous potential to promote patient-centered care, the communication of PROs to patients and to clinicians in practice is challenging. Realizing the full benefits of measuring PROs in clinical applications requires that PRO data are communicated accurately, and that clinicians and patients understand what the scores mean. The wide variation in PRO measurement and reporting strategies has created tremendous heterogeneity of PRO reporting formats, and this heterogeneity has interfered with the understanding and use of PROs in practice. We have identified seven key themes that emerged from the evidence base and have reviewed consensus recommendations for PRO data visualization. Readers interested in implementing these recommendations can find resources to assist their efforts on the PROTEUS Consortium website.

11.8 Questions That Can Be Used for Learning/Testing

- What are some of the challenges in creating effective data visualization strategies that are particularly relevant to the communication of patient-reported outcomes?
- Patient-reported outcomes have potential applications both in routine clinical practice and in research applications such as clinical trials reporting. What considerations for effective data visualization are common to both applications? What considerations are most relevant for only clinical practice applications? What considerations are most relevant only for research applications?

11.9 A Topic for Discussion That Can Be Used in Teaching

Some PRO visual data summaries can be confusing, because for some instruments, higher scores sometimes indicate better outcomes functioning (e.g., physical functioning) or poorer outcomes (e.g., nausea or fatigue scores). Why are some instruments designed this way, and what strategies can be useful in overcoming the inherent data communication challenge?

11.10 Further Reading List

The following list presents literature that reinforces and expands on the contents of this chapter.

- *Evidence-based, stakeholder-driven recommendations for PRO data presentation:*
- Snyder C, Smith K, Holzner B, Rivera YM, Bantug E, Brundage M, PRO Data Presentation Delphi Panel. Making a picture worth a thousand numbers: recommendations for graphically displaying patient-reported outcomes data. Qual Life Res. 2019;28:345–56.
- www.theproteusconsortium.org: "Checklist for Graphically Displaying PRO Data"; Video overview: "Displaying PRO Results Graphically: Overview of Recommendations" and other resources.
- *Examples of methods for helping patients and clinicians interpret PRO scores*
- Shi Q, Mendoza TR, Cleeland CS. Interpreting patient-reported outcome scores for clinical research and practice: definition, determination, and application of cutpoints. Med Care. 2019;57:S8–12.
- Cook KF, Cella D, Reeve BB. PRO-bookmarking to estimate clinical thresholds for patient-reported symptoms and function. Med Care. 2019;57:S13–7.
- Jensen RE, Bjorner JB. Applying PRO reference values to communicate clinically relevant information at the point-of-care. Med Care. 2019;57:S24–30.
- *Examples of qualitative exploration into the challenges in PRO data interpretation*
- Brundage MD, Smith KC, Little EA, Bantug ET, Snyder CF, PRO Data Presentation Stakeholder Advisory Board. Communicating patient-reported outcome scores using graphic formats: results from a mixed-methods evaluation. Qual Life Res. 2015;24:2457–72.
- *Examples of reviews of graphic data presentation in general:*
- Shah P, Freedman EG, Vekiri I. The comprehension of quantitative information in graphical displays. In Shah P, Miyake A, editors. The Cambridge handbook of visuospatial thinking. New York: Cambridge University Press; 2005. p. 426–76.
- Weissgerber TL, Winham SJ, Heinzen EP, Milin-Lazovic JS, Garcia-Valencia O, Bukumiric Z, Savic MD, Garovic VD, Milic NM. Reveal, don't conceal: transforming data visualization to improve transparency. Circulation. 2019;140:1506–18.

11.11 Research in Context

Patient-reported outcomes (PROs) can be applied in three contexts to promote patient-centered care: an individual patient's PRO data can inform his/her clinical care; PRO results from research studies can directly inform patients (e.g., in educational materials or decision aids) about the impacts of diseases and treatments, and the same PRO results from research studies can inform clinicians in their decision-making and researchers in their work. Given the wide variation in how PROs are summarized and reported within each of these contexts, a modified Delphi process was used to develop stakeholder-driven, evidence-based recommendations for PRO data display for each context. Key issues addressed by these recommendations in all contexts were directionality (i.e., whether higher scores were better/worse outcomes) and conveying score meaning. Issues specific to individual patients included representation (bar charts vs. line graphs) and highlighting possibly concerning scores (both in absolute terms and changes over time). Issues specific to research study results presentation included handling normed data, conveying statistically significant differences, illustrating clinically important differences, and displaying proportions improved/stable/worsened. The recommendations are summarized in this chapter, and are more fully described by Snyder and colleagues [20].

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12 Cross-Cultural Considerations in Health-Related Quality of Life in Cancer

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12.1 Introduction

Culture can be defined as an integrated pattern of learned beliefs and behaviors that can be shared among groups and can include thoughts, styles of communicating, ways of interacting, views on roles and relationships, values, practices, and customs [1]. "Ethnicity" incorporates the notions of a shared social, cultural, or religious background that is distinct and passed on between generations leading to a shared identity. With the world becoming a global village, one's interaction with people from different ethnic and cultural backgrounds is inevitable.

Furthermore, rising globalization through factors such as immigration [2] influence on one's professional, personal, spiritual, and social lives. Therefore, it is no surprise that globalization will have its effects on the provision of healthcare in relation to cultural awareness and cultural competence.

Cultural competence in healthcare is a term that has been a subject of much research and speculation in the last decade. With healthcare providers (HCPs) seeing more patients of diverse backgrounds, there is a need to explore any beliefs that patients might have regarding their treatment, which could increase adherence to treatment and help them achieve satisfactory health outcomes [1]. Research has shown that culture can shape beliefs and attitudes about health, illness, death and dying, expectations concerning death and diagnosis, decision-making roles of the patient and caregivers, and perceptions regarding complementary and alternative medicine [3]. Therefore, HCPs need to be culturally aware of such beliefs not just to address them but also to avoid stereotyping patients according to their cultural or racial backgrounds.

Despite advancements in oncology, the diagnosis of cancer is still seen as a life-changing event that can have a significant impact on the HRQOL of these patients [4]. The concept of cultural competence can become even more challenging when dealing with cancer, as an HCP must navigate through complex topics of breaking the diagnosis, treatment options, management options, pain management, and at times end-of-life care, not just with the patient but at times with their family as well.

This chapter will enable the readers to: (a) understand the role and influence of sociocultural factors on the perceptions regarding the HRQOL of cancer patients and their families; (b) recognize the importance of providing culturally competent care to achieve greater patient satisfaction; (c) identify and address the challenges faced by both HCPs and researchers while

encountering cancer patients of different cultural backgrounds; (d) understand the concepts of cross-cultural adaptation, equivalence, validity, and their utility in designing inclusive research tools and instruments that capture the cultural diversity and generate more nuanced insights regarding its impact on HRQOL.

12.2 Role of Culture in Cancer Patients' Perceptions and Attitudes Toward the Disease

12.2.1 Perceptions of Cancer Pain

Pain is a common and significant health problem for cancer patients, which can affect their HRQOL. Research has shown that 59% of patients on anti-cancer treatment, 33% of patients after anti-cancer therapy, and 64% of patients with advanced-stage disease or metastatic cancer can experience pain. In addition, adequate pain relief can be achieved in 70–90% by using appropriate guidelines for improving HRQOL [5, 6].

The bio-cultural model of pain proposed by Bates [7] explores the role of social learning in the variability of pain across cultures. The model hypothesizes that psychological and physiological processes of pain can be influenced by social learning from family and group membership in an individual's lives, which in turn can affect the perception and modulation of pain. When a person experiences a pain stimulus, the individual's past memories and cultural beliefs might determine whether the pain impulse reaches the level of awareness, and this may affect the person's perception and response to it [8]. Consequently, a person's interpersonal relationship and exposure to social patterning determine whether certain reactions of pain will receive approval or disapproval in their cultural and social context.

The above model of pain can be extended to understand the different pain "experiences" across cultures in cancer. In a systematic review to compare pain barriers via the Wards Barrier questionnaire, Asian cancer patients generally had higher barrier scores than Western patients [5]. A possible explanation for this difference can be that without adequate knowledge of the disease, Asian patients might believe cancer pain to be a universal and inevitable consequence in patients with cancer [9].

Patients from certain ethnicities might not complain of pain or present with the complaint when it is more severe. Additionally, some cultures that value stoicism (such as Asian) might hinder patients from expressing their pain to avoid being perceived as being weak. Certain South Asian studies have identified traditional medicine as the first-line medication sought for the alleviation of pain [10]. Another cross-cultural study found that some individuals belonging to Middle Eastern and Asian cultures attributed the pain to be a result of the "evil eye" and would want to "leave fate in the hands of God" [11]. These reasons can be a factor in the late presentation of such patients to allopathic HCPs for pain control.

It is only when the HCPs will be aware of certain perceived barriers toward receiving pain management that they will be able to address them. Therefore, it is crucial for HCPs to carefully assess the patient's perception of pain symptoms arising from cancer in a contextual way to allow for therapeutic discussions, early intervention, and a better HRQOL.

12.2.2 Religion and Perception of Disease

Religion and spirituality can also influence the perception of disease in cancer patients. Certain religions, such as Hinduism, have a concept of "karma" [3] or punishment for a person's past deeds in life, which patients correlate with their comorbid conditions, such as morbidities of cancer.

Among Muslims, the disease is not seen as punishment for their past sins but more of a way to learn endurance to improve their spirituality and connection to God [8]. If not adequately provided with their treatment options, patients might feel that this is an inevitable part of their disease trajectory, giving rise to a fatalistic attitude toward cancer.

It might be important to note that religious predilection should not always be considered a barrier to obtaining anti-cancer care. In a qualitative study conducted on African-American patients, religious beliefs and practices positively influenced attitudes toward the disease and helped in enduring treatment [12]. Another systematic review found a positive correlation between spiritual well-being and HRQOL in cancer patients [13].

Furthermore, both religious and secular-minded people might have different outlooks on disease [14]. For example, a religious person might either believe they are created by and loved by God or think they have let him down. A secular person might view the same situation differently by recalling that they still have their family or friends by their side. A qualitative study carried out in England found religious congregations such as church congregations to be a source of emotional and social support to patients and revealed that the experience of living and dying from cancer might be seen as a "spiritual investment" by some Black Caribbean patients which would be rewarded in the afterlife [15]. However, the HCPs should try to be well informed of the patient's attitude toward his/her disease in a religious and spiritual context to counsel them regarding any thoughts that might negatively affect their HRQOL.

For example, patients who believe their cancer is due to punishment in the patient's past deeds and are distressed about the fact can be reminded of any silver linings, this disease might have to offer, such as a good prognosis, time to spend with family, or in any spiritual activity that might bring satisfaction to them. However, this can only be achieved by evaluating the patient in such a context, and perhaps a multidisciplinary approach to a patient can allow a psychosocial evaluation to take place if needed.

12.2.3 Influence of Cultural Factors on Use of Complementary or Alternative Medicine

The decision to opt for complementary or alternative medicine (CAM) can be influenced by one's ethnic background [16]. CAM can consist of a wide range of approaches, ranging from herbal medicine, homeopathy, yoga, as well as spiritual counseling or prayer.

The use of CAM is related to how well connected the patient and their family might feel toward their cultural heritage. People of different ethnicities can prefer other modalities of CAM such as herbal medicine by Chinese, spiritual counseling by Native Hawaiians, and religious and spiritual healing by Filipinos [9].

Certain CAM therapies are of a communal nature and make the patient feel connected to their family and community [17]. These therapies can also facilitate patients in coping with certain perceptions about their disease, such as it being related to "pay-back" for their past deeds or being able to have a "peaceful passage to the afterlife" [17].

It is important for an HCP to at least have knowledge about common CAM therapies prevailing in the cultural context in which they practice, as it reportedly improves patient satisfaction [18]. The shifting paradigm of healthcare toward a patient-centered approach necessitates an empathic attitude of the HCP and perhaps an effort to negotiate the integration of certain CAM therapies while adhering to conventional medicine.

12.2.4 Role of Family and Gender Influencing Cancer Care

In certain cultures, health-related decisions may be primarily seen as the duty of the family in order to alleviate the patient's stress related to the disease and to protect him/her from the additional burden of making more difficult decisions related to the disease.

The role of family members in a patient's disease trajectory varies across cultures. Certain traditional societies in South Asian Countries, such as India, have more significant involvement of family members in healthcare decisions [3]. Family involvement in a patient's chronic illness, such as cancer, can support the patient logistically, physically, and emotionally. At times where out-

of-pocket healthcare systems or inadequate health insurance exist, strong family ties can result in the financial support of the patient as well.

While such family dynamics have their advantages, they can also result in the patient's autonomy being compromised through collusion. Collusion in a medical context can refer to selective disclosure or non-disclosure about the patient's diagnosis. The intention behind collusion is usually to protect an already ailing patient from further setbacks. A study in South India reported that 40% of cancer patients were not informed about their diagnosis [19].

Gender roles in traditional societies also affect collusion through assumptions that women are not able to make important decisions. Another Indian study reported that two-thirds of women with cervical cancer had their diagnosis concealed by husbands and family members [20]. In the Indian family scenario, a paternalistic approach pervades during each stage of healthcare where a "responsible" family member, usually a patriarch, has the greatest influence on medical decisions [21].

These roles can at times be challenged during times of illness, creating disparities in HRQOL. A study conducted in India noted married women diagnosed with cancer to have lower HRQOL compared to unmarried women, which is reflective of a married woman's status in a traditional household [22]. Certain cultures expect women to take up the role of caregivers or home-makers, and a cancer diagnosis might deprive them of this role, and in turn, the demand for the social support the patient might need.

In contrast, Western societies which run on a comparatively individualistic approach favor disclosure of diagnosis. In the United States, the patient rights movement compels HCPs to inform patients of the diagnosis. Studies have reported an 80% disclosure of information in Austria, Denmark, and other European countries [3].

The difference in collusion between traditional and non-traditional societies has been argued to stem from differing collective versus individualistic approaches, respectively [23]. These approaches have influenced which principle of bioethics is more valued in these healthcare systems. The individualistic society puts greater value on the principle of autonomy, which is seen in full disclosure, candid conversations about the disease, end-of-life care planning, and informed consent. A society that values the collectivistic approach is more influenced by the principles of beneficence and non-maleficence, which at times can become a barrier to informing patients about their diagnosis and can result in the patient playing a more passive role in their cancer journey.

However, does disclosure of diagnosis cause distress among patients as perceived by certain societies? Collusion is found to be associated with poorer HRQOL in India, with 95% of cancer patients in a study saying that they prefer to know about the diagnosis [24]. However, a study in Iran showed that disclosure of diagnosis results in a poorer HRQOL among cancer patients [25].

It is challenging for the HCP to ascertain which ethical principle will benefit the patient in such a situation. The disclosure of information might be necessary for, let us say, a patient who is the sole breadwinner of the family as the treatment to follow will be financially taxing. The distress caused while breaking diagnosis might be lessened by integrating disclosure in the patient-HCP interaction in a culturally appropriate way. For example, filial societies can have adult offspring present while breaking bad news for emotional support. At times, negotiation might be needed between family members and the HCP into breaking bad news in a stepwise manner with multiple clinical encounters. Such measures might be cumbersome but necessary, keeping the patient's best interests and HRQOL at hand before and during management.

12.2.5 Language Barrier in Communication

The close relationship between language and culture makes it an important aspect to consider in cross-cultural cancer care. A language barrier can refer to both the HCP's inability to speak to patients and a poor understanding of how different ethnic groups use language to indicate emotions [26].

Language discordance between the HCP and patient is shown to be associated with worse psychological and physical health outcomes [27]. Linguistic considerations can be challenging for an HCP as the nature of counseling can change with different languages. For example, in Pakistan, it is customary to use the word "Insha'Allah," meaning "as God wills" when talking about future plans, a practice also seen by HCPs when counseling patients about the prognosis of their disease. However, the English Language does not have an appropriate replacement with the same cultural value as "Insha'Allah," and HCPs seeing an immigrant from Pakistan might not be able to counsel patients in a way that is culturally relevant to them.

In cancer treatment, a disease is already seen as a life-changing event, communication amidst language barriers can prove to be more difficult. Certain cultures have negative connotations associated with the word "cancer" or "depression" [3], proving to be challenging for both the HCP and the patient. For the HCP, it can be hard to screen a patient for depressive symptoms if no exact word exists in the person's native tongue. For the patient, language incompetency with the HCP might be a barrier to expressing symptoms related to the disease or any distress they might be feeling.

There have been a few suggestions to overcoming language barriers, the most practical of which seems to be an interpreter that acts as a third party between the HCP and the patient. However, interpreters need to be skilled in forming a rapport with the patient to voice their concerns. Some doctors prefer relatives of a patient to take up the role of the interpreter. Unfortunately, this might displace the patient or a more immediate family member from the decision-making role [28], transferring it to the moderator. In such a scenario, the patient's preference should be asked first as to who they would want as a moderator in one's efforts to best move forward in providing patient-centered care.

The other suggestion involves "Language matching," which matches the patient to an HCP who is of a similar ethnic background or who might know the patient's native language, in the hope of a more effective HCP-patient encounter. With globalization, one might argue that the need for a culturally diverse workforce [29] is even more necessary than before. This requires a drastic change in not just the healthcare but also the health education system, with a particular focus at the grass-root level.

Perhaps a more short-term solution is to involve social health workers and mobilize community workers to cater to the patients from a specific ethnic minority. A study in Israel showed [26] that cancer patients who are from a different cultural background than the HCP, such as Arab, are "matched" to an Arabic social worker by some HCPs in order to form a "continuous relationship."

More work needs to be done in developing culturally competent healthcare systems that will aim to improve HRQOL in cancer patients. In addition to the oncologists and nurses, community health workers or social workers should be mobilized and trained to build a rapport with such patients, to screen them for certain physical and psychological symptoms which the primary team might fail to pick.

12.2.6 Concept of Death and Dying

According to the WHO [30], "cancer is the first or second leading cause of death before age 70 years in 91 of 172 countries." The diagnosis of cancer brings with it distress regarding mortality and needs to be discussed with patients (see also Chap. 14, this volume). In addition, end-of-life care should also be planned.

Additionally, "preparedness for death" might entail different meanings for different patients and caregivers. Chaturvedi et al. [21] encompass medical, psychosocial, spiritual, and practical aspects related to preparedness for end of life and argues that it can involve (1) knowing about signs and symptoms that may present in the later stages of disease; (2) discussing emotions and sharing grief with family and friends; (3) prayer and talking about the meaning of death; and (4) arrangements regarding finances (written will) or funeral arrangements.

However, the concept of death has different connotations across cultures. Paradoxically, societies influenced by fatalism, such as Asian societies, might not always be ready to talk about end-of-life care openly. People belonging to certain cultures might have superstitions regarding communication about death. A systematic review [31] revealed that certain people from Chinese and Filipino backgrounds think it is "bad luck" to talk about death, and talking about it will evoke it. The review reported that in hospice care for such patients, they might prefer not talking about their illness but being more optimistic about their present health. This can place a challenge for HCPs more acclimatized to Western medicine where a more direct approach to such topics of communication is the norm.

Conversations in such cases regarding end-of-life decisions should be modified to the patient's needs. After evaluation of what the patient perceives death, dying, and palliative or hospice care as, language can be modified to prevent distress or confusion. An example is from an adaptation of an advance care planning guide for young Brazilian patients with cancer [32] in which participants, when asked, felt that instead of saying "when my end-of-life is near," using the phrase "when the moment that the end of my life is near arrives" felt less direct and more optimistic. On the other hand, when the sample guide was revised by patients in Australia, the section on asking for forgiveness was considered irrelevant to them in the secular Australian society [32].

The need to be culturally competent while discussing death becomes even more critical in a palliative setting, as an HCP might need to educate the patient regarding advance care planning. A systematic review revealed that non-white ethnicities in the United States are associated with lower acceptability to advance life care planning than white ethnicities [33]. Another study in New Zealand showed that people from Maori and Pacific Cultures are reluctant to discuss death, which might translate to them not having faith that the person will live [34].

Other possible barriers to receiving end-of-life care can be autonomous versus a collective approach to medical decision-making. Asian cultures, as opposed to European cultures, are more likely to lean toward family decision-making regarding advance life care planning [35]. A study in Taiwan revealed that 82.7% of DNR orders are signed mostly by family members rather than the patient themselves [36], with delay in patient involvement in end-of-life care being one of the factors for the discrepancy.

Therefore, the HCP needs to assess the patient's ideas and attitudes about the prognosis of his/her disease and involve the patient in decision-making based on their disease trajectory and response to treatment. After evaluating the patient's needs and wishes regarding his/her illness, the provider needs to have an end-of-life care discussion with simple language avoiding medical jargon and use the potential influence of religiousness/spirituality in end-of-life care discussions. Existing culturally sensitive guidelines can be used for a culturally competent patient encounter [37].

Furthermore, HCPs should inquire and be aware of any end-of-life rituals that the patient expects to go through. Open communication about death and end-of-life care may reveal any wishes that the patient has regarding burial, cremation, Do Not Resuscitate (DNR) orders, and dying at home or in the hospital. Doctors in palliative care in certain South Asian countries or paternalistic settings might face the difficulty [3] of choosing on the patient's behalf, as they are seen as the authoritative figures in the matter. In any situation, it is essential to consider and respect the patient's needs and wishes on the matter securing the patient's dignity, conserving his/her HRQOL, and facilitating rather than dictating his/her decision.

12.3 Suggested Frameworks and Strategies to Address Cross-Cultural Challenges and Considerations

12.3.1 Explanatory Model of Disease

The greatest challenge of caring for any ethnicity is arguably the balance that needs to be achieved

between being culturally ignorant and also oversimplifying the values of that social group. One such way, proposed by Betancourt et al. [1], is to explore certain aspects in the clinical encounter, including any:

(a) Cross-cultural issues
(b) Meaning of illness to the patient
(c) Social context
(d) Negotiation to improve adherence to the disease

There can be various cross-cultural aspects that need to be taken into account during a clinical encounter. Given the variety of cultures/subcultures/ethnicities that an HCP can be exposed to, it is best to keep in mind certain aspects of cultural issues to prevent misunderstandings, such as:

(a) Style of communication including both verbal and non-verbal cues such as eye contact and physical touch.
(b) Exploring any potential mistrust and prejudice that the patient might have against the doctor, for example, any mistrust regarding racial provider bias [33] from past experience.
(c) Assessing the family dynamics and decision-making dynamics of the patient. As discussed before, this will have an impact on diagnosis disclosure, treatment planning, further counseling, and at times end-of-life care and advance care planning.
(d) Traditions, customs, and spirituality that might affect the patient's perception of disease.
(e) Sexuality and gender issues.

Furthermore, the meaning of illness to the patient should also be explored. Patients might have certain perceptions about the disease that can be associated with their societal beliefs. A cross-cultural study [34] conducted in Australia and Vietnam showed that a higher percentage of Vietnamese patients reported their cancer being caused by "bad luck or fate," highlighting a possible association with the fatalistic beliefs prevailing in the culture. Additionally, poor diet was also identified as the most frequently perceived cause of cancer, highlighting the importance of diet in the Vietnamese culture. Therefore, it is important to assess the patient's perception of their illness to prevent any misunderstanding and added distress or guilt the patient might have in an effort to improve HRQOL.

Determining the factors that make up the patient's social environment, such as socioeconomic status, support, literacy, dominant language, social stressors, which will impact the patient's perception, attitude, and action toward his illness, is also essential. An excellent social history will encompass all these aspects so that the healthcare team can move forward with the context in mind.

Cross-cultural differences can cause disagreements between patients and HCPs. A "negotiation" is going beyond the conventional authoritative role that an HCP plays but more of an understanding role that makes sure that the patient and involved caregiver(s) are well informed of the disease's nature, prognosis, treatment plan. A negotiating nature of the encounter will value the patient's beliefs.

The explanatory model of disease proposed by Betancourt can be extended to cancer care as well, encompassing aspects that will be essential in any cross-cultural clinical encounter [1].

12.3.2 Health Belief Model

The health belief model (HBM) [35] was initially developed in 1952 by social psychologists in the United States Public Health Service to explain and predict preventive health behavior, to explain the widespread failure of people to participate in programs, and to prevent and detect disease [38–40]. Later, it was modified and extended to study people's responses to symptoms [41] and their response to a diagnosed illness [42]. The HBM consists of six descriptors as follows:

(a) Perceived susceptibility: patient's assessment of the risk of getting a disease.
(b) Perceived severity: patient's assessment of individual illness.

(c) Perceived barriers: patient's assessment of influences that might discourage the proposed action from managing illness.
(d) Perceived benefits: patient's assessment of positive consequences of the promoted outcome.
(e) Cues to action: perceived factors that might help the patient take the recommended action.
(f) Self-efficacy: ability to successfully execute behavior that is recommended.

The health belief model can be extended to provide an understanding of patient perceptions and actions regarding cancer. A systematic review evaluating cervical cancer screening among immigrants and ethnic minorities in the United States [36] revealed that African, Hispanic, and Middle Eastern minorities had preconceived notions about pap smears threatening women's virginity. Only when one enquires about patient health beliefs is when such thoughts are revealed and can be counseled for.

Extending the health belief model to tertiary care in cancer, it is imperative to know about, for example, a patient's perceived severity of the disease to handle disclosure of the diagnosis and further treatment plan tactfully. A patient's beliefs, such as pursuing conventional and alternative medicine, might hinder them from opting for chemotherapy. Unless the HCP is aware of this perceived barrier, he/she cannot reach a middle ground of perhaps integrating certain CAM into conventional medical therapy. Certain cues to action for treatment might be the patient's family or caregivers that can at times influence the patient's decision, as we have previously discussed for certain cultural settings. The self-efficacy of the patient can also be determined, and in an appropriate context, the concept of support groups, social workers, or informal caregivers can facilitate the patient and aim to improve his/her HRQOL.

12.3.3 Strategies to Breaking Bad News

The need to break the bad news to cancer patients can arise at any point of the treatment. It can arise right at the beginning from the diagnosis of disease to a later phase, such as failure of further response to treatment or preparing a patient and family for advance life care planning. The complex situations surrounding the disease trajectory coupled with cross-cultural differences among different patients that might present to an HCP necessitates the need for a tactful and culturally competent approach to disclosing bad news.

The ABCDE model of breaking bad news proposed by Koenig and Gates-Williams [37] is a tool that can be used to assess the Attitudes, Beliefs, Context, Decision-making style, and Environment that surrounds patients.

A description on how to use ABCDE in a clinical encounter is as follows:

(a) Attitudes of patients and families: Explore the patient's ideas toward, for example, truth-telling, diagnosis disclosure, death, and dying. Healthcare workers should educate themselves about ideas regarding cancer common to ethnic groups commonly encountered in their practice.
(b) Beliefs: Explore patient's and family's religious and spiritual beliefs regarding the disease, any alternate medicine influenced by those beliefs, beliefs about the afterlife.
(c) Context: Ask the patient about their historical and political context, for example, place of birth, immigration status, socioeconomic status, languages spoken, and comfortable with.
(d) Decision-making style: Determine the level of authority the patient has in decision-making. Will medical decision-making be primarily done by the patient or collectively as a family or by one member of the family.
(e) Environment: Explore and utilize any aids that can help the HCPs be more culturally competent such as translators, healthcare workers from the same community, religious leaders, community leaders, other family members.

Another descriptive study done in South Africa explored strategies to communicate the diagnosis of osteosarcoma to patients [43]. It proposes additional use of visual aids, metaphors, and the need to negate any cultural health mis-

conceptions of their cancer happening due to "bewitchment." The study also mentioned the need to prepare the person before-hand or "set the stage" for breaking bad news by assessing how much the patient knows and informing the patients for reasons for performing diagnostic tests and warning the patient of the possibility of cancer throughout the diagnostic process.

12.4 Cross-Cultural Considerations in HRQOL Research

The relationship of culture with an individual's perception of their health is multi-layered. Literature shows that cultural beliefs profoundly impact the HRQOL of cancer patients, particularly as they approach the end of their life [44]. As societies become progressively multiethnic, providing evidence-based culturally competent care to the patients can become very challenging for the providers and health systems. Most of the research tools currently being used to evaluate HRQOL outcomes are designed for English-speaking western countries [45] and therefore do not capture the factors affecting the HRQOL of culturally diverse patients. There is a need for developing new tools or modifying pre-existing survey instruments to bridge this gap. There are many different approaches to this problem. The "particularists" approach assumes that cultures vary significantly in their understanding of HRQOL, and therefore instruments designed for one culture cannot be used in another. The "absolutists" approach suggests that health and disease are experienced the same way in all human beings regardless of their cultural or linguistic identity. Finally, the "universalists" approach recommends that careful modifications allow similar instruments to be used across different cultures [46].

12.4.1 Particularist Approach: Starting from Scratch

From the lens of a particularist approach, every culture should need an assessment tool designed specifically for that population. It assumes there is minimal overlap in the understanding of HRQOL. This can be useful when assessing certain behaviors, such as sexual behaviors only observed in certain cultures [47]. This will allow for high face and content validity and make the instrument very user-friendly as the administration mode can be tailored to the population [48]. However, this strategy is very resource and time intensive, especially in low middle-income countries (LMICs).

12.4.2 Absolutist Approach: Utilizing a Pre-existing Tool

The "absolutist" approach dictates that there is little to no difference in how HRQOL is perceived across cultures. This approach leaves little to no room for including domains that may be more important for some cultures and may retain components that other cultures cannot relate to or consider crucial. For example, autonomy is highly valued in North American societies. But this may come across as selfish in Eastern societies as people in these cultures tend to value family and cohesiveness over individualism [49].

It should also not be assumed that the psychometric and other properties will remain the same regardless of the population. The first Spanish translation of the Sickness Impact Profile for the United States' Spanish-speaking population had low construct validity [50]. The advantage of translation of existing tools followed by further psychometric testing is that it is very cost-effective as it utilizes instruments that have already been used elsewhere and allows for cross-culture comparisons, which is especially important when HRQOL is being studied in international studies or clinical trials. This is especially true for societies that are linguistically and culturally similar [48].

12.4.3 Universalist Approach: Joining Forces

This approach acknowledges that there are some similarities and differences across cultures that need to be reflected in the assessment tools. This

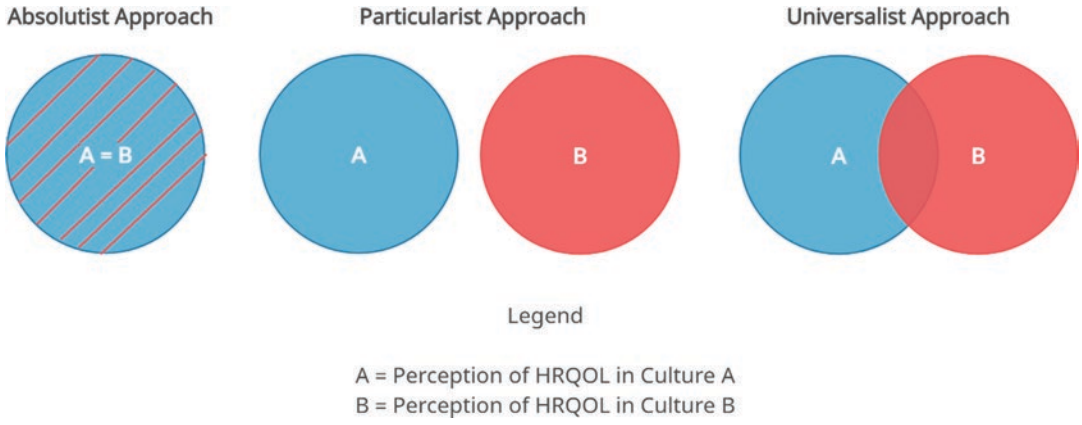

Fig. 12.1 Perceptions of HRQOL across different cultures: Absolutist, Particularist, and Universalist approaches

involves creating a team of researchers from different parts of the world to develop an instrument that covers the general and culture-specific domains. The WHOQOL group is an example of this approach, with representatives from different cultural groups contributing equally to the design of HRQOL tools [51]. This is a meticulous process where each facet is analyzed in the context of every culture, and questions are added, removed, or modified depending on their cultural relevance [47, 51]. Another example is the European Organization for Research and Treatment of Cancer (EORTC), an organization that has been active for over 50 years and studies the HRQOL of cancer patients in 37 countries across all European countries and Australia, the United States, and Canada [52]. It has shown high reliability, validity, and responsiveness [52–54]. This strategy is also very resource and time intensive and might not allow for comparisons across cultures if there are too many modifications.

A diagrammatic representation of all aforementioned approaches is depicted below (Fig. 12.1).

12.5 Aspects to Consider in Cross-Cultural Adaptation, Validation, and Translation

Cross-cultural adaptation (CCA) is a way to achieve cultural equivalence by understanding the difference between the cultures being studied [55–57]. On the other hand, cross-cultural validation aims to ensure that the new instrument functions the same way as its old counterpart and carries the same functions [58]. There are many aspects to consider when validating a tool across different cultures, as highlighted by Corless et al. [59].

12.5.1 Cultural Relevance

It is essential to evaluate whether components of a HRQOL instrument are culturally relevant or critical to the target audience. Target participants living in war and conflict-ridden zones, abject poverty, or severely underserved areas may have a different expectation of HRQOL. They may find some components to be irrelevant. In cultures where discussing the impact of the disease on sexuality or reproductive function is stigmatized, patients may feel uncomfortable sharing this information with the researchers even if that affects their HRQOL significantly. It is essential to approach these issues with sensitivity. For example, in adapting the Ferrans and Powers QLI (HRQOL Index) for Taiwanese culture, the question "How satisfied are you with your sex life?" became "How satisfied are you with your intimacy with your spouse" [60]. Additional questions about the extended family's role were also included as it significantly impacted the individual's well-

being [60]. Similarly, alternative therapies are a part of many cultures. Still, the exact nature and type of treatment may be different, and therefore it is crucial to focus on the therapies specific to the population.

12.5.2 Phenomenon of Interest

Certain phenomena may be more critical to HRQOL in one culture than the other. Sometimes, the same phenomenon may be interpreted differently in different populations [61]. The equivalent of low "energy" in Chinese is low *"jingshen,"* which also includes spiritual vigor in its meaning [46]. Similarly, the term "emotional problems," when translated into German and French, carries the connotation of psychiatric illness [61].

12.5.3 Culture Versus Nation

Nation and culture are anthropological terms with different meanings. Many cultures can coexist within one country, and many different nations can have similar cultural origins [62]. While cultures are centered around a common language, sometimes there can be slight differences in speakers of the same language living in different countries [59].

12.5.4 Achieving Equivalence

Cross-cultural adaptation of a research tool should not be limited to just forward and backward translations to ensure equivalence of language. It can fail to capture the essence of the question being asked. The concept of equivalence can be very vague and broad. There are many different terms used in literature with no standard definition. These types include conceptual, semantic, technical, psychometric, and others. Cross-cultural comparisons can only be made once these types of equivalences are established, which can only happen after prerequisites, such as a valid translation method, are satisfied [47].

12.5.4.1 Conceptual Equivalence

While there is no consensus on what constitutes conceptual equivalence, many agree that it is an essential condition to satisfy before other equivalences can be achieved [63]. Acquadro et al. define conceptual equivalence as a type of equivalence "achieved when answers to the same questions reflect the same concept. In other words, a construct is recognized as being conceptually equivalent cross-culturally if it can be meaningfully discussed in each of the cultures concerned" [64]. The concept being studied should not only be comparable but also carry equal importance in each culture. For example, surgical scars are likely to have a higher impact on the HRQOL in cultures that highly value cosmetic appearance even though they cause disfigurement in all [47]. This can be established in qualitative interviews and focus group discussions.

12.5.4.2 Semantic Equivalence

Semantic equivalence determines "whether the same expression exists in the other language" [65]. It is interchangeable with functional equivalence [66]. There are two components to semantic equivalence, that is, denotative and connotative sameness. Denotation refers to the literal or primary meaning of a term, whereas connotation refers to abstract meaning or intention conveyed by the word in addition to its primary meaning. Certain idioms, proverbs, or other culture-specific phrases may lose their essence in a forward-backward translation and require the use of various procedures and tools to achieve semantic equivalence [67].

12.5.4.3 Technical or Operational Equivalence

Technical or operational equivalence refers to the congruence of the method of obtaining data [68]. Sharing information about one's HIV status, sexuality, or financial situation may be considered inappropriate in many cultures. This is especially true if the questionnaire is interview-based rather than self-administered, which can be necessary for populations with low literacy. Questionnaires using Likert-type scales or visual analog scales might not be familiar to people living outside highly industri-

alized countries, and participants may require additional assistance to understand them. In Buddhist cultures, respondents may not answer honestly about feelings of depression or dissatisfaction with treatments so as not to offend the researchers [47]. Many respondents in Islamic cultures may find it hard to communicate with researchers from the opposite gender, especially in matters of reproductive health [47]. Another definition of technical equivalence is in terms of grammar and syntax of the measure. For example, when the Diagnostic Interview Schedule for Children was developed in Puerto Rican Spanish, several questions could be translated into more concise sentences than English without losing meaning [69].

12.5.4.4 Psychometric Equivalence

Psychometric equivalence is also referred to as measurement equivalence. Psychometric equivalence is satisfied when the instruments have similar validity, reliability, and responsiveness in different cultural groups (see also Chap. 7, this volume). Reliability refers to the consistency with which the same results are produced when the tool is used on different occasions [70]. Responsiveness refers to the ability of the tool to accurately detect if any changes have occurred over a period of time [71]. Validity extent to which a concept is accurately measured [70]. It is of three major types, that is, content validity, construct validity, and criterion validity. Content validity refers to the extent to which a study instrument is "relevant to, and representative of, the targeted construct it is designed to measure" [72]. Construct validity is defined as the "extent to which a research instrument measures the intended construct" [70]. Finally, criterion validity is "the extent to which a research instrument is related to other instruments that measure the same variables" [70].

12.5.4.5 Scalar/Metric Equivalence

Another commonly mentioned type is scalar or metric equivalence. Some scholars argue that these are two different entities, where metric equivalence refers to "the extent to which the adapted measures place individuals who are similar with regard to the HRQOL states being measured on the same point in the continuum of score" [66]. In contrast, scalar equivalence refers to whether "a given rating or response is equated to the same degree of the construct across cultures (e.g., a rating of 5 on a life satisfaction item must refer to the same degree of satisfaction across cultures)" [66, 73, 74]. Similarly, the difference between excellent, good, or fair may not be as intuitive for everyone.

Table 12.1 summarizes the various types of equivalences and key questions that need to be considered.

Table 12.1 Types of equivalence in cross-cultural adaptation in HRQOL research

Type of equivalence	Key questions to consider
Conceptual equivalence	Can a construct be meaningfully discussed in each of the cultures concerned? [64]
Semantic equivalence	Does the same expression exist in the other language? [65]
Technical equivalence	Is there a congruence of the method of obtaining data? [68]
Psychometric equivalence	Do the instruments have similar validity, reliability, and responsiveness in different cultural groups? [71]
Reliability	Are the results consistent? [71]
Content validity	Is the instrument representative of the targeted construct it is designed to measure? [72]
Construct validity	To what extent does the research instrument measure the intended construct? [70]
Criterion validity	To what degree does the research instrument relate to other tools that measure the same variables? [70]
Metric equivalence	What is the extent to which the adapted measures place similar individuals on the same point in the continuum of score? [66]
Scalar equivalence	Does the given rating or response equate to the same degree of the construct across cultures? [66]

12.6 Challenges and Limitations of Cross-Cultural Considerations in HRQOL in Cancer

Even though HRQOL is gaining importance as an outcome of interest in clinical trials and practice [65], cross-cultural aspects are yet to be

considered while interpreting these outcomes. A study on Latina breast cancer survivors in the United States revealed that they, on average, had lower HRQOL, experienced depression, and unsupportive relationships at higher rates than their non-Latina counterparts [66]. This phenomenon is not limited to Latina patients, as it is also seen in the immigrant population in general [67]. Another study evaluating the HRQOL of patients in a multinational trial on breast cancer showed systematic differences in the HRQOL of patients across different cultures receiving the same treatment regimen [68].

Additionally, the process of cross-cultural adaptation of an instrument can be very time-consuming and resource intensive [75]. The International HRQOL Assessment project carried out a cross-cultural adaptation of the SF-36 questionnaire for 14 countries, the process of adaptation alone took over 3 years. A shortage of PhD programs and Ph.D.-prepared HCPs in LMICs and lack of funding is a significant impediment to progress. Culture itself, as described by Epner et al., "is a very elusive and nebulous concept, like art" as it can vary significantly within a group depending on the age, gender, and other socioeconomic factors; therefore, the separation between cultural competence and stereotyping can be very tricky [76]. There are many blind spots in the current literature owing to the paucity of studies on the impact of culturally competent care on the perceived HRQOL of the patients or other patient-reported outcomes [77].

12.7 Implications of and Recommendation for Cross-Cultural Considerations in HRQOL in Cancer and the Way Forward

Many researchers argue that cultural competence is a core tenant of patient-centered care [69]. Patients who consider their provider to be aware of the cultural nuances are more likely to be satisfied with their care [70]. Culturally sensitive care is patient-centered care that keeps in mind the patient's attitudes, beliefs, context, decision-making style, and environment throughout the trajectory of their disease [36]. However, implementing such care is often challenging as people from different racial and ethnic backgrounds can co-exist in one setting. This is further complicated by the country's immigrant and refugee status, adding to the region's cultural diversity.

A few recommendations for culturally competent practice and research are as follows:

Teaching Cultural Competence Changing demographics of patients demands that providers be well versed with the different cultural groups they are interacting with. Teaching cultural nuances to HCPs and researchers early in the medical training ensures that patient-centered care does not get compromised.

A Multidisciplinary Approach to Cancer Care A multidisciplinary approach to cancer care should not only consist of oncologists, palliative care specialists, surgeons, and psychiatrists/psychologists but also community health workers, skilled translators to aid in counseling patients to improve compliance. Where appropriate, spiritual or religious figures can be involved to endorse allopathic management or counsel about patient's fears regarding any aspects of their disease in a way that will be more familiar and comfortable for them.

Call for More Research Further studies, of both qualitative and quantitative nature, can help gain more insight into the cultural factors that influence cancer patients' HRQOL. Developing new survey instruments or cross-culturally adapting existing tools for various diseases is another area that requires additional funding and research. Strengthening collaboration among researchers across countries and cultures and creating avenues for such cooperation is needed. Additionally, considering cultural aspects when designing clinical trials that incorporate HRQOL

as an outcome and increasing participation of minorities can help generate evidence that guides clinical practice.

Standardization of the Process Epstein et al. identified 31 different methods for cross-cultural adaptation but found no consensus [55]. It was also found that various methods emphasized different aspects. Some were focused on the technique of translations, others on focus groups of cultural experts, etc. There was no evidence in the literature that one approach was better than the other. Therefore, there is a need for standardizing the process of cross-culturally adapting a research instrument to increase the quality and efficiency.

12.8 Conclusion

In conclusion, cultural differences should be kept in mind by both HCPs and researchers while evaluating a patient's HRQOL. Socio-cultural factors such as religion, family roles, and language play an important role in understanding the illness from a cross-cultural lens. These factors might also significantly impact any stage of a patient's disease trajectory, including reactions to breaking bad news, decision-making regarding treatment, perception, and attitudes toward treatment and management, and advance care planning. Therefore, both researchers and HCP's need to have a culturally sensitive approach in their respective studies and clinical encounters to better understand and address any culture-specific concerns that affect the HRQOL of patients across communities.

It is important to instill qualities of cultural competence in HCPs, particularly for those who are early on in their training for effective execution of these principles in their practice. The essence of good communication in a cross-cultural setting is a sense of empathy and willingness to understand the patient's values and beliefs, as highlighted in the theoretical models and the frameworks. In addition, institutes providing cancer care should promote a multidisciplinary approach involving psychologists/psychiatrists and social workers to screen patients for unmet needs of psychological and social support. Additionally, to improve patient compliance to treatment, the benefit of collaborating with community leaders, religious and spiritual figures, and practitioners of alternative medicine should be assessed and implemented where possible. For a researcher, an inclusive approach to research is the key to generating insights and ensuring cultural competence in HCPs. Various approaches can be utilized to design instruments and survey tools that capture the understanding of HRQOL in different cultural contexts, with each approach having its strengths and weakness. Additionally, the cross-cultural adaptation of questionnaires needs to be standardized across the board by devising translation methods and achieving equivalences.

12.9 Questions That Can Be Used for Learning/Testing

1. Why are cross-cultural considerations important in identifying the health-related quality of life in patients with cancer?
2. What factors influence the perception toward cancer or any other chronic disease?
3. Should the process of cultural adaptation and development of questionnaires be standardized?
4. How can one identify which approach – particularist, absolutist, or universalist – will best fit the study purpose?
5. How can cultural competence be inculcated in clinical education?

12.10 A Topic for Discussion That Can Be Used in Teaching

How can healthcare providers keep a balance between the cross-cultural considerations and the ethical principles of beneficence and non-maleficence in cancer patients?

12.11 Further Reading List

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12.12 Research in Context

A study reviewed the existing literature for methodologies on cross-cultural adaptation of study instruments across disciplines. There was no consistency in the methods mentioned in any of the 31 studies. The guidelines vary greatly and were mostly based on the prior experience of the researchers and not scientific evidence. Different types of equivalences were focused upon in the articles. Some guidelines recommended having an expert committee to ensure equivalence, while others recommended focused group discussions with the target audience. The stance on back translations was a subject of much controversy, with some authors considering it indispensable and others not recommending it.

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Quality of Life and Mortality

13

Amélie Anota

Contents

13.1 Introduction

In oncology clinical trials, quality of life (QoL) is considered a patient-centered endpoint, in addition to overall survival. A benefit of using experimental treatment is generally targeting QOL when no significant benefit in terms of overall survival has been reached. While overall survival remains the gold standard to assess the clinical benefit of a treatment in phase III randomized clinical trials, QoL can be more important than overall survival in specific populations or situations like, for example, in elderly cancer patients or palliative care and at the end of life. The choice between quantity and quality of life has thus been raised. However, QoL is not independent to survival. The association between QoL and mortality has been established since a long time: patients

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with poor QoL will be at risk to early death compared to patients with high QoL. Two patients with similar disease characteristics but with different QoL level will not have the same chance to survive. Lots of studies have been conducted in oncology on the association between QoL, at baseline or change over time, and survival. This chapter will thus present a summary of research conducted in this area, the possible limitations as well as implications for both clinicians and researchers. The choice between quality and quantity of life is finally discussed (see also Chap. 2, this volume).

This chapter will enable readers to: (a) be aware that QoL is associated with survival in many cancer sites; (b) be familiar with research already conducted in this field; (c) identify important methodological concepts to consider when conducting research on the prognostic value of QoL; and (d) be familiar with shared decision-making and patients' preference regarding QoL over quantity of life.

13.2 Association Between Survival and QoL

The choice between QoL and quantity of life is not completely independent. Indeed, it seems intuitive that a patient with a bad QoL level will be less likely to survive than another patient with the same disease stage but a significantly better QoL level. This means that the QoL level can be associated with the duration of survival of the patient. An important part of research in this area has been conducted regarding the association between QoL level and overall survival. This association could be investigated at the time of cancer diagnosis, before treatment starts, or during the treatment course. It has been demonstrated for various cancer sites and therapeutic settings that the QoL level at baseline is a prognostic factor of overall survival. The baseline could correspond either to the cancer diagnosis or to the QoL assessment at the time of study entry before the treatment starts.

To illustrate, the association between QoL and survival can be graphically represented as in Fig. 13.1.

In this figure, we can see that the survival duration differs according to baseline QoL level of the patients. This representation was based on data from a randomized clinical trial performed in elderly patients with non-small cell lung cancer [1]. Three groups of patients were constructed based on their baseline QoL level considered as low, intermediate, or high. As reported in the figure, the median overall survival was equal to 5.3 months for patients with low QoL level at baseline, 8.2 months for patients with intermediate QoL level, and 14.5 months for patients with high QoL level. This emphasizes the importance of the prognostic value of QoL level. The global QoL/health status dimension of the European Organisation for Research and Treatment of Cancer (EORTC) QLQ-C30 questionnaire was used (see also Chap. 5, this volume).

Since QoL is a multidimensional concept, different dimensions of QoL can be associated with survival. A bad QoL could correspond to the presence of a number of symptoms, bad physical functioning, or an overall bad QoL level for example. The QoL domains associated with survival can vary according to the cancer site. Table 13.1 summarizes studies recently published regarding the prognostic value of QoL level on overall survival.

Table 13.1 does not aim to be exhaustive but to present examples of studies in various cancer sites. In this table, we can notice the variety of the domains associated with survival as well as the diversity of questionnaires used. However, due to the variability of the questionnaires used, it can be difficult to compare the results between studies. For example, two studies on metastatic colorectal cancer have been identified (Table 13.1). Both studies used data from randomized clinical trials on previously untreated patients [2, 3]. The first study conducted by Diouf and colleagues used the generic EuroQoL EQ-5D questionnaire to assess QoL and identified that both mobility and pain dimensions are independently associated with overall survival of the patients [2]. The second study conducted by Mol

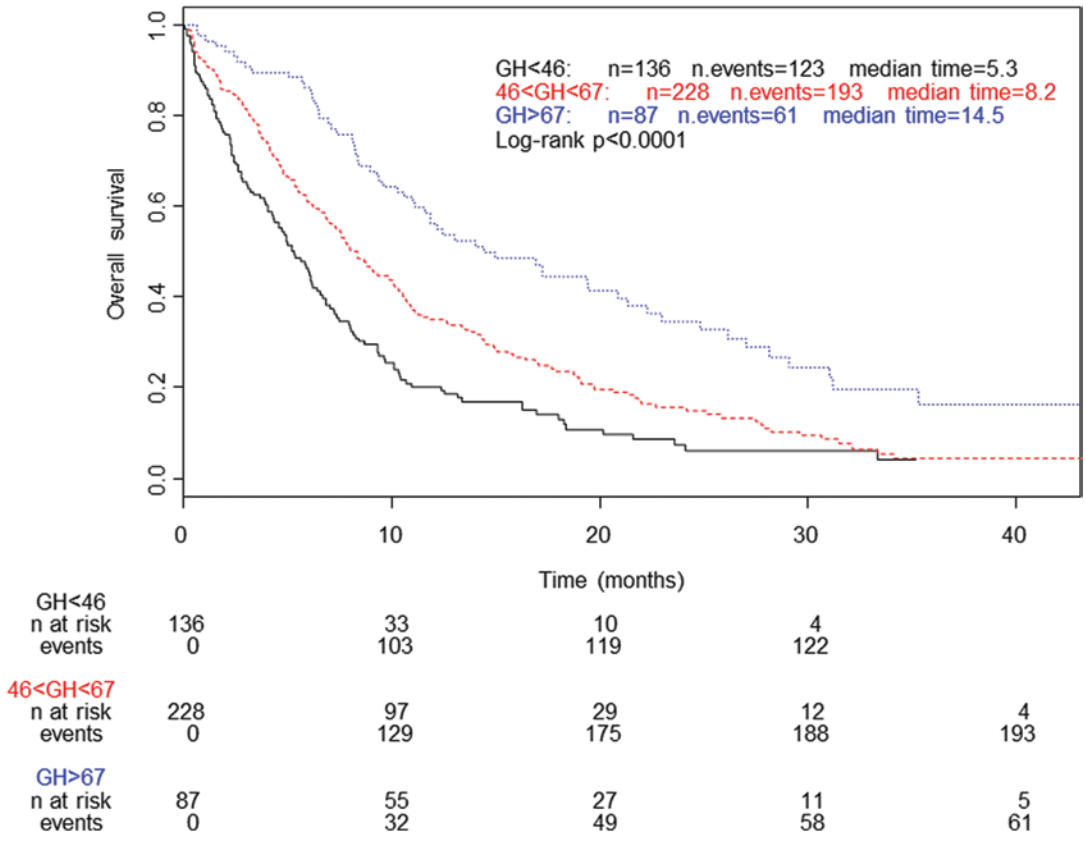

Fig. 13.1 Overall survival stratified according to the global health (GH) status score from the QLQ-C30 questionnaire. (Reprinted from Fiteni [1], Copyright (2021), with permission from Elsevier)

and colleagues used the EORTC QLQ-C30 and identified the physical functioning dimension as significantly associated with survival [3]. The heterogeneity in the questionnaires used compromises the comparison of the results, and affect all studies about QoL data.

Due to the heterogeneity of results observed, systematic reviews and meta-analyses were conducted in order to confirm previous results [4–8]. One well-known meta-analysis conducted by Quinten and colleagues was done on individual data from randomized clinical trials of the EORTC [8]. This meta-analysis was conducted on 30 randomized clinical trials from 11 cancer sites. The main cancer sites were lung (six trials), melanoma (four trials), and prostate cancer (four trials). This review was limited to the EORTC QLQ-C30 cancer-specific questionnaire. Authors highlighted that, adjusting for age, gender, cancer sites and the World Health Organization performance status, among other parameters, the physical functioning, pain, and appetite loss dimensions of the QLQ-C30 significantly increased the predictive accuracy of prognosis of overall survival by 6%.

Another systematic literature review performed by Gotay and colleagues included 39 studies published between 1989 and 2006 [4]. The main cancer sites were lung (31%) and breast (21%) cancer. The EORTC QLQ-C30 questionnaire was the most frequently used QoL questionnaire. In 36 studies, at least one QoL dimension was significantly associated with survival. The most frequently independent predictor of overall survival for the majority of cancer sites were the global QoL dimension (38%) and the physical functioning dimension (28%) of the QLQ-C30.

Table 13.1 Examples of studies recently published regarding prognostic value of quality of life on survival and domains of QoL significantly associated with survival in multivariate model

First author and year of publication	Type of data	Cancer setting	Questionnaires	QoL domain significant	Sample size
Braun et al. 2011 [51]	Observational	Non-small cell lung cancer	QLQ-C30	Global QoL; physical	1194
Cella et al. 2012 [52]	RCT phase III	Metastatic renal cell carcinoma	FKSI-15; FACT-G	No multivariate model	750
Chase et al. 2012 [53]	RCT phase III	Advanced and recurrent cervical cancer	FACT-Cx; BPI	Physical	991
Diouf et al. 2014 [2]	RCT phase III	Metastatic colorectal cancer	EQ-5D	Mobility; pain	620
Eilard et al. 2018 [54]	Observational	Hepatocellular carcinoma	QLQ-C30; QLQ-HCC18	Fatigue; nutrition	205
Fiteni et al. 2016 [1]	RCT phase III	Elderly non-small cell lung cancer	QLQ-C30	Global QoL	451
Guo et al. 2018 [55]	Observational	Nasopharyngeal carcinoma	QLQ-C30; QLQ-H&N35	No significant QoL score in multivariate model	554
Li et al. 2017 [56]	Observational	Hepatocellular carcinoma	QLQ-C30; QLQ-HCC18	Pain; physical functioning; fatigue	517
Mol et al. 2016 [3]	RCT phase III	Advanced colorectal cancer	QLQ-C30	Physical functioning	635
Peters et al. 2014 [57]	Observational	Recurrent high-grade glioma	FACT-Br; FACT-F	Fatigue	237
Phippen et al. 2017 [58]	RCT phase III	Advanced epithelial ovarian cancer	FACT-O	Composite of physical and functional well-being subscales and the ovarian cancer subscale	1152
Roncolato et al. 2017 [23]	RCT phase III	Platinum-resistant ovarian cancer	QLQ-C30; QLQ-OV28	Physical; abdominal/gastrointestinal symptom	326
Staren et al. 2011 [59]	Observational	Breast cancer	QLQ-C30	Role	1511
Thompson et al. 2018 [60]	Observational	Aggressive lymphoma	FACT-G; LASA	Functional, physical, social, Global FACT-G score, LASA overall	701
Vickers et al. 2016 [9]	RCT phase III	Advanced pancreatic cancer	QLQ-C30	Physical	569
Yang et al. 2016 [61]	Observational	Head and neck cancer	QLQ-C30; QLQ-H&N35	Dyspnea; appetite loss	141
You et al. 2011 [62]	Observational	Locally recurrent rectal cancer	FACT-C; BPI	Pain	105

RCT randomized clinical trial

An update of this systematic review was recently conducted [6]. This systematic review included 44 phase II or phase III randomized clinical trials including 13 different cancer types. Main cancer sites included were lung (20%) and head and neck (14%) cancer. The most frequently used QoL questionnaire was the EORTC QLQ-C30 followed by the Functional Assessment of Cancer Treatment (FACT) questionnaire (see also Chap. 6, this volume). Confirming the results obtained by Gotay and colleagues, the authors found that the most frequently QoL domains associated with survival were physical functioning (39%) and global QoL (34%).

A systematic review and meta-analysis that was not limited to randomized clinical trials was also conducted by Efficace and colleagues [7]. They identified a total of 138 studies published between 2013 and 2018 including at least one QoL domain in the multivariate model. The majority of studies were on lung (30%) and genitourinary (20%) cancers. The authors pointed out that the QLQ-C30 questionnaire was the most frequently used questionnaire in 41% of the trials. The physical functioning dimension of the QLQ-C30 was also the most frequently prognostic QoL factor in the multivariate model.

As highlighted in all these systematic literature reviews and meta-analyses, studies on the prognostic value of QoL on survival are performed in a large variety of cancer sites. However, research is particularly important in advanced cancer patients as highlighted in Table 13.1 and in recently published systematic literature reviews [6, 7].

13.3 Association Between Survival and Quality of Life's Change Over Time

Less studies investigated the association between QoL change over time and survival. The methodology of these kind of studies are more difficult than those only focused on baseline QoL level, due to the longitudinal nature of QoL assessment.

For example, one study investigated the association between baseline QoL and change from baseline with overall survival among advanced pancreatic cancer patients [9]. This study was based on data from an international randomized controlled trial which included 569 patients. QoL was assessed using the EORTC QLQ-C30 questionnaire. Both QoL level at the time of study entry and change from baseline in terms of physical functioning was associated with overall survival, after controlling for other confounding factors. An improvement in physical functioning after 8 weeks of treatment was associated with a longer overall survival. This study was thus limited to QoL change at one follow-up assessment.

The association between change of QoL and survival was also explored in advanced colorectal cancer patients [10]. A total of 396 patients were included in a cohort conducted in a single cancer care center of the United States. QoL was assessed using the EORTC QLQ-C30 questionnaire prior to any treatment and after 3 months of treatment. The change in QoL was explored subtracting baseline score to those observed at 3 months. A change of at least 10 points was considered as a clinically significant difference. The authors showed that an improvement in physical functioning was associated with longer survival of patients. Indeed, they also found that an improvement of social functioning was associated with a shorter survival of the patients. This result was quite surprising since other studies generally found a reverse effect of improvement in any QoL domain.

Another study investigated the association between change in QoL and survival in localized head and neck cancer patients [11]. This study used data from 540 patients included in a randomized clinical trial conducted in Canada. Patients were followed up during radiotherapy. QoL was assessed using the EORTC QLQ-C30 cancer-specific questionnaire and the Head and Neck Radiotherapy Questionnaire validated for this set of patients [12]. Questionnaires completed at baseline and 6 months after the end of the radiotherapy were used. The change in QoL was explored subtracting the score at 6 months to that observed at baseline, before treatment

started. The change in physical functioning was the most significantly associated factor with overall survival, after controlling for baseline confounding factors.

All these studies are limited to the change of QoL observed at one given follow-up time-point. Indeed, these studies do not consider a longitudinal QoL assessment. The QoL change was a priori introduced as another covariate in Cox regression models, thus not using a time-dependent variable. The relationship over time between QoL and survival could be better appreciated through the use of other modeling including a joint model [13]. To illustrate, a study explored this model among advanced cancer patients treated in a cancer center of the United States [14]. Patients were included in the weeks following their cancer diagnosis. A longitudinal assessment of QoL was performed using the FACT-G cancer-specific questionnaire. A joint model was thus used to assess the longitudinal association between QoL and survival using the FACT-G total score as an indicator of global QoL. The authors highlighted that, at each follow-up time-point, an improvement in QoL was associated with an increase of survival. Indeed, the trajectory of QoL over time was also highly significantly associated with survival.

13.4 Limitations of Current Studies

One important remark we can make regarding studies on the prognostic value of QoL on survival is that they had generally not been designed for that purpose. Indeed, authors generally used existing data to conduct research on the prognostic value. In the systematic review performed by Efficace and colleagues, 73% of the identified studies investigated prognostic value in secondary data analysis [7].

One consequence of this is that an important part of the studies comes from randomized clinical trials. However, clinical trial settings with usually stringent inclusion criteria are thereby not reflecting the large majority of patients who are typically seen in clinical practice. Indeed, most of cancer patients above a certain age, with comorbidities or already receiving some medications, have not been represented in clinical trials. Consequently, the generalizability of findings from randomized clinical trials to patients seen in real-life practice is limited. Results on cohort or real-world data have thus been proposed [15]. These results provided valuable information and confirm the prognostic value of QoL on survival.

Another consequence of the use of existing data to conduct research about the prognostic value of QoL is that the sample size of the studies was not determined specifically for that purpose. This is not a huge problem as long as the researchers justify the sample size required for this analysis. This is not systematically done in this area of research. Efforts of the researchers should still be made to systematically justify the sample size or statistical power of their results [6]. The heterogeneity of the sample size is also illustrated in Table 13.1, where sample size of studies presented varies from 105 to 1511 patients.

The introduction of QoL data in prognostic models also implies some methodological challenges. One of the important challenges is the multicollinearity between QoL scores [16]. In fact, most of QoL questionnaires are multidimensional scales, generating a variety of QoL scores. A correlation between these scores, or at least some of these scores, is often observed. For example, an association between fatigue and physical functioning is widely demonstrated [17]. The well-known EORTC QLQ-C30 questionnaire is often used in oncology clinical trials and to study the prognostic value of QoL on overall survival, as already mentioned. This questionnaire explores various functional and symptomatic QoL domains. A correlation between these domains, including physical functioning and fatigue, is thus generally observed (see also Chap. 17, this volume). A solution for taking into account this multicollinearity should thus be proposed. One strategy can be to propose a statistical analysis strategy to take into account multicollinearity between QoL scores. For example, a simulation study recently compared the performance of different modeling strategies to estimate the prognostic value of QoL, taking into

account the collinearity between QoL scores [18]. The authors highlight that the Cox regression model using proportional hazard assumption including all variables but penalized with the Ridge regression was the most suitable model to account for multicollinearity. This is not, at this time, the most frequently used method to estimate the prognostic value of QoL on survival. To date, the classical Cox regression model seems to be the most widely used method. In a recent systematic review restricted to randomized clinical trials, 95% of the identified studies used the Cox regression model [6]. A selection of variables using univariate analysis is generally conducted. Then, the assessment of correlation between all eligible variables for the multivariate model is at least recommended in order to avoid the problem of multicollinearity.

Another alternative is to select a priori interesting variables, and consequently interesting QoL domains. This can be done according to a priori hypothesis. For example, making the assumption that fatigue is a relevant information for a set of patients can be reasonable [19]. The selection of potential prognostic QoL domains was done in 55% of the studies identified in the systematic review conducted by Mierzynska and colleagues [6]. Recently, the US Food and Drug Administration also recommended a set of QoL domains relevant to be assessed within clinical trials [20]. This was done in order to be sure of capturing a treatment effect on the patients' well-being, and no other effect that can bias the interpretation of the results. They recommend to focus on symptomatic adverse events and physical functioning. These recommendations, however, are very controversial and sparked reaction from the community of researchers [21]. Indeed, the physical functioning is not the unique functional domain of importance for cancer patients.

Another strategy proposed to account for multicollinearity is to use a summary score instead of each individual QoL score. For example, a summary score of the EORTC QLQ-C30 was recently proposed. Researchers thus explored the ability of this score to be a prognostic value of survival in various cancer sites [15]. They found that this summary score has a strong association with mortality. Indeed, authors concluded that this summary score appears to have more prognostic value than the global QoL/health status score assessed with two specific items of the QLQ-C30 or any other specific scale of the QLQ-C30.

As other studies using QoL data, one limitation, or at least a challenge to consider for these studies is the impact of missing data (also see Chap. 10, this volume), at baseline and over time [6]. Particularly, for advanced cancer patients, missing QoL data can be associated with poor QoL level and thus poor prognosis. It is thus important to collect information about the reason for missing QoL data. In the systematic review of Mierzynska and colleagues, only 11% of the identified trials reported the reasons for missing QoL data at baseline [6]. An analysis comparing patients with available QoL and those with no available QoL data is also useful when the proportion of missing QoL data is important. This analysis can be done according to baseline clinical and socio-demographic characteristics. A comparison in terms of overall survival is also particularly important. Researchers have compared these profiles of patients and found shorter overall survival among patients with no available QoL information [22]. It is also informative for confirming that QoL level is associated with survival.

A validation of the results is finally required to confirm the results observed. First, an internal validation could be performed, using bootstrap sampling for example. Then, an external validation is required confirming the results using an independent sample. This external validation is rarely done. For example, an external validation was done in a study exploring the ability of QoL to predict overall survival in women with platinum-resistant ovarian cancer [23]. External validation was also done in a study exploring prognostic value of fatigue at diagnosis among patients with myelodysplastic syndromes [24]. In the systematic review of Mierzynska and colleagues, only one study (2%) reported an external validation with an independent study [6]. In the systematic review of Efficace and colleagues, only 22% of identified papers validated their model, corresponding either to internal or external validation [7].

13.5 General Implications

One immediate implication of the association between QoL and mortality is that QoL should be included in most of existing prognostic scores. However, studies aiming to demonstrate the prognostic value of QoL on survival generally do not go to the end of this process. Studies in this context are sparse but have been proposed for various cancer sites. For example, one study proposed the development of a new prognostic score incorporating patient's self-reported fatigue based on existing prognostic scores for patients with myelodysplastic syndromes (see the Research in Context box for more details). For patients with palliative hepatocellular cancer, a study also explored the ability of QoL to improve the classification of patients proposed with several available prognostic sores used in practice [22]. They demonstrated that both fatigue and diarrhea QoL scores from the QLQ-C30 should be added to the Cancer of the Liver Italian Program classification in order to optimize the performance of the classification.

The limitation of the addition of QoL in existing prognostic factors can be due to the underconsideration of QoL by clinicians. Another possible explanation is that QoL tools could not be appropriate for a rapid utilization in clinical practice and then in prognostic scores. Take the example of a global summary QoL score from the FACT-G cancer-specific questionnaire that is a prognostic factor of survival for cancer patients. This summary score involves administrating to the patient, a 27-item long questionnaire and the use of a statistical software to generate the summary score. This should be an argument to not use a summary score within a prognostic score. One other consequence is that a single item, although less informative or accurate, could be more adapted to be introduced in prognostic scores. For example, some studies have demonstrated that the fatigue scale from the QLQ-C30 is a prognostic factor for survival. This will require the administration of the QLQ-C30 questionnaire to all patients, or at least the three items assessing the fatigue dimensions. The use of a single item such as the visual analog scale of fatigue could give quite similar results while being less restrictive to patients. This single item of fatigue assessment was significantly associated with overall survival in elderly cancer patients [25].

13.5.1 Implications for Clinicians

The association between QoL and mortality suggests to clinicians to take into account the QoL level of their patients in their clinical practice along with tumor and biological parameters [26]. This should be done in order to ensure the best possible care to the patients as well as the greatest chance to survive. The assessment of QoL in clinical practice remains generally explorative and at the research stage (see also Chap. 11, this volume). A number of studies explored different strategies to assess QoL in routine care since a decade ago [27–29]. These studies have demonstrated a benefit of this implementation in terms of symptom control, quality of life, and communication between physician and patient [27, 30]. The impact of this monitoring assessment on overall survival has been studied in a limited number of these studies [31, 32].

One study conducted by Basch and colleagues focused on outpatient chemotherapy from various advanced solid tumors treated in a single center of the United States [30]. Primary cancer sites were genitourinary, gynecologic, breast, and lung cancer. A total of 766 patients were randomized to report a list of common symptoms via tablet computers or to receive usual care. Overall survival was a secondary outcome and was recently published [31]. The monitoring of key common symptoms led to an improvement of overall survival of 5 months, with a median of overall survival equaling to 31.2 months in the symptom monitoring group versus 26 months in the control group.

Another study was conducted by Denis and colleagues [32]. This study was a multicenter, randomized, controlled trial conducted in France. It included advanced lung cancer patients, nonprogressive, with last treatment less than

3 months before randomization in this study. Patients were randomized for web symptom monitoring versus usual care. Symptom monitoring consisted of self-report of 7 key symptoms (appetite loss, fatigue, pain, cough, and breathlessness), with a graduation on a 0 (no symptom) to 3 (major symptoms) scale. Overall survival was the primary endpoint and showed significant results at the time of interim analysis conducted when the trial ended. Then after, an update of the overall survival with a 2-year follow-up of the patients was published [33]. In this update, the median overall survival was equal to 22.5 months in the symptom monitoring intervention group versus 14.9 months in the control group, confirming the benefit from self-reporting of symptom from patients.

Both studies are limited to symptom monitoring and not overall QoL including emotional components among others. Other studies aiming to assess overall QoL should be pursued in order to completely assess their impact in terms of overall survival.

13.5.2 Implications for Researchers

The association between QoL and mortality suggests to researchers to take into account QoL as a stratification factor in randomized clinical trials. At this time, most of phase III randomized clinical trials use the performance status, either from World Health Organization or the Karnofsky index, as a stratification factor to ensure the balance between groups regarding prognostic factors [34]. The use of QoL as stratification factor instead of the performance status could increase the comparability of the treatment arms allowing to take into account the multidimensional component of QoL. Recently, clinical trials have begun to use a QoL score as a stratification variable. This has advantages, if QoL is an endpoint of the trial, to ensure that all patients will have available QoL data at baseline. One difficulty is using the most suitable QoL score from multidimensional questionnaires and the best threshold to dichotomize patients between those with high versus those with low QoL level.

Another research implication is related with QoL analysis. Since QoL is associated with mortality, the analysis of QoL data should be done in light of survival data. This is of particular importance for studies with advanced cancer patients. Several strategies can involve consideration of death, including joint modeling [13] and time to deterioration analysis [35].

13.6 Choice Between Quality and Quantity of Life

While there is now an unquestionable association between QoL and mortality, the choice between quality and quantity of life remains unclear in particular circumstances. In fact, it has been recognized that QoL can be more important to the patient than length of life depending on patient's characteristics and disease stage (see also Chap. 2, this volume). This is the case of two specific populations, namely, elderly cancer patients and palliative care cancer patients.

Elderly cancer patients can be prepared for losing a certain quantity of their life in order to maintain their good QoL level [36]. A workshop was thus initiated with the EORTC in order to define the best endpoint to consider in clinical trials involving elderly cancer patients [37]. The conclusion was that quality of life, as well as functional status and independence, should be assessed as key endpoints in clinical trials with elderly cancer patients.

In palliative care, the main objective is also to maintain a good QoL level for the patients. In order to measure goals of care for this group of patients, a single-item visual analog scale was thus developed, ranging from 0 (QoL is all that matters) to 100 (length of life is all that matters) [38]. This questionnaire can be used in clinical practice in order to facilitate the discussion between the patient and the clinician.

A systematic literature review was also performed to identify factors influencing patients' preference to quality or quantity of life among cancer patients [39]. Aging was the main factor associated with preference for QoL over length of life. The type of cancer as well as gender or having children

was not associated with a preference between quality and quantity of life in this review. Not surprisingly, the authors highlight that patients with better health status would prefer quantity of life while those with lower health status would prefer QoL.

In order to counterbalance quality with quantity of life, utility measures have been developed. Two methods have thus been proposed to estimate quality adjusted survival, namely, standard gamble and time trade-off. Both methods are based on patients' choice between two situations. In standard gamble, we ask the patients to choose between being ill during a certain period of time or to receive a treatment which can either be a success or be fatal to the patient. In time trade-off, patients generally need to choose between length of life and QoL [40, 41]. These utility measures are particularly used in medico-economic studies (see also Chap. 15, this volume). One utility well-known questionnaire is the generic EuroQoL EQ-5D questionnaire [42]. This questionnaire is the most widely used in oncology studies aiming to investigate patients' utility value. However, it was not specifically designed for cancer patients. The EORTC has thus developed a new questionnaire based on the QLQ-C30, namely, the QLU-C10D, to derive a health-state classification system [43]. In comparison to the EQ-5D, the QLU-C10D seems to be more capable to detect clinical known-groups and will be more and more used in future studies [44].

In the area of shared decision-making, preference for QoL is of particular importance [45, 46]. Tools to help both clinicians and patients to detect time where quality of life will become more important than quantity of life are of particular importance. We already mentioned a single-item visual analog scale to facilitate discussion. As another example, the Quality/Quantity Questionnaire was also developed to assess patients' preferences between quality and quantity of life in order to help with treatment options [47].

13.7 Conclusion

Numerous studies have demonstrated the association between quality of life and mortality in various cancer sites and at different time-points since diagnosis. It is now time to consider quality of life in routine clinical practice in order to improve quality-of-life level of the patients and, at the end, increase their chance to survive. Finally, while QoL is not independent to mortality, the choice between QoL and quantity of life is of particular importance in the area of shared decision-making in order to choose the best treatment strategy for patients.

13.8 Questions That Can Be Used for Learning/Testing

- A researcher wants to determine the prognostic value of QoL in a given set of cancer patients. What are the key methodological challenges that the researcher should consider before and during the analysis?
- Two studies explored the prognostic value of QoL at diagnostic level among colorectal cancer patients. Both studies used the same QoL questionnaire. The first one showed that the social domain of QoL was the single QoL dimension significantly associated with survival. The second found that the physical domain of QoL was significantly associated with survival. How can we explain this difference in results? What could be done in order to confirm (or not) the results observed?

13.9 A Topic for Discussion That Can Be Used in Teaching

In order to implement QoL assessment in routine clinical practice as well as patients' preference between quality and quantity of life in elderly cancer patients, you should, as a researcher, propose a protocol for a new study. You thus, need to decide which QoL and patients' preference questionnaires to use in clinical practice, the time of assessment, and the method of administration. Please develop your protocol with this information reported and using a clear justification for your choices.

13.10 Further Reading List

We invite interested readers who need more details to read the following papers or guidelines:

- Regarding the choice between quality of life and mortality:
  - Williams CP, Miller-Sonet E, Nipp RD, Kamal AH, Love S, Rocque GB: Importance of quality-of-life priorities and preferences surrounding treatment decision making in patients with cancer and oncology clinicians. Cancer 2020, 126:3534–3541.
  - Meropol NJ, Egleston BL, Buzaglo JS, Benson AB, 3rd, Cegala DJ, Diefenbach MA, Fleisher L, Miller SM, Sulmasy DP, Weinfurt KP: Cancer patient preferences for quality and length of life. Cancer 2008, 113:3459–3466.
- For the implementation of QoL in routine clinical practice, the EORTC proposed a guideline available on the EORTC website: Wintner, L. M., Sztankay, M., Aaronson, N. K., Bottomley, A., Giesinger, J. M., Groenvold, M., ... & Holzner, B. (2016). A manual for the use of EORTC measures in daily clinical practice. Available on the EORTC Website (https://qol.eortc.org/manuals/).

13.11 Research in Context

In 2015, Efficace and colleagues have published studies on the prognostic value of quality of life on survival among patients with myelodysplastic syndromes [19]. The primary objective of this study was to explore the ability of the self-reported fatigue level to be a prognostic value of overall survival for these patients in a multivariate model including the existing International Prognostic Scoring System (IPSS) prognostic score. This IPSS score is widely used in clinical practice as well as in clinical trials. It allows to distinguish four risk groups: a low risk, intermediate-1-risk, intermediate-2-risk, and high-risk [48].This study was specifically designed to explore the prognostic value of self-reported fatigue. Therefore, the sample size was estimated based on this primary objective. A total of 265 patients had to be included in order to highlight an increase of at least 1.10 hazard ratio (HR) for every 10-point increase in the baseline fatigue level of the patients, with a statistical power of 80% and a type I error rate of 5%. Fatigue was assessed using the EORTC QLQ-C30 cancer-specific questionnaire which is widely used and validated in this setting of patients [49, 50].A total of 280 patients were finally included in this international, multicenter, observational, cohort study from 2008 to 2012. Median overall survival was 17 months (95% confidence interval (CI) 15, 19). In univariate analysis, the baseline fatigue level was significantly associated with overall survival with a univariate HR of 1.130 (95% CI 1.080, 1.190). In multivariate analysis, after controlling for other factors associated with survival among the IPSS prognostic score, the baseline fatigue level remained significantly associated with overall survival with a HR of 1.110 (95% CI 1.040, 1.170) and a p-value of 0.0007.More recently, the authors published a second paper on the development of a new prognostic score based on the IPSS and incorporating baseline self-reported fatigue level [24]. In fact, the objective was not only to demonstrate the prognostic significance of quality of life, but to take into account the fatigue level of the patient in determining the corresponding risk group of the patient.The authors then proposed a new prognostic score, namely, the FA-IPSS(h), increasing the C Harrell index form 0.565 for the IPSS to 0.610, reflecting an improvement in the discrimination ability. This new prognostic score allows to distinguish between three risks groups:

- Risk 1, corresponding to patients with IPSS intermediate-2 and low fatigue level (<45 points), with a median of overall survival of 23 months in the development cohort.
- Risk 2, corresponding to patients with IPSS intermediate-2 with high fatigue (≥45 points), and patients with IPSS high-risk with low fatigue (<45 points), with a median of overall survival of 16 months in the development cohort.

Risk 3, corresponding to patients with IPSS high-risk and with high fatigue level (≥ 45 points), with a median of overall survival of 10 months in the development cohort.The cut-off of 45 points for the fatigue level was retained to maximize the predictive performance for overall survival.An external validation was also performed in order to validate these results with an independent cohort of patients. Results were confirmed in this cohort showing the importance to now use this new patient-centered prognostic score for patients with myelodysplastic syndromes.

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Decision-Making in the Context of Funding Cancer Therapy

14

Barbara de Graaff and Ingrid Cox

Contents

14.1 Introduction

This chapter will provide the reader with an overview of how measures of quality of life are incorporated into health economic evaluations in the context of cancer care. The chapter briefly introduces health economics and why it is impor-

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tant, followed by the various approaches to measuring quality of life that can be used in health economic evaluations. The focus then turns to a type of cost-effectiveness analysis that incorporates both quality and quantity of life, called a cost-utility analysis. Finally, important metrics such as quality-adjusted life years (QALYs) and incremental cost-effectiveness ratios (ICERs) are outlined, and how these can be interpreted.

This chapter will provide the reader with an understanding of (a) an introduction to health economic evaluations and why they are conducted; (b) how quality of life is incorporated into health economic evaluations; (c) approaches to measuring quality of life for health economic evaluations; (d) quality-adjusted life years (QALYs); (e) incremental cost-effectiveness ratios (ICERs), and (f) willingness-to-pay thresholds.

14.2 Health Economics

New cancer treatments are emerging at a rapid pace and are revolutionising treatment for many patients. A feature of many of these new treatments, such as immunotherapies, is the high cost. For example, in 2017 the per patient cost (in US dollars) of the lung cancer drug pembrolizumab was $87,000 in the US; $34,000 in the UK; $31,000 in the Netherlands; and $27,000 in Germany [1].

In many countries, such treatments can be accessed at either a subsidised cost or for no cost at all. In such settings, governments and/or health insurers pay for the treatment on behalf of the patient. Whilst this is an excellent outcome for the patient, it is also important to consider the costs to government and insurers.

In most settings, government is the main body paying for health services, so will be the focus of this chapter. Examples of government bodies providing free or subsidised access to treatments for patients include the UK's National Health Service (NHS), Australia's Medicare system, Canada's Medicare system, France's French Health Insurance (FHI), and Norway's National Insurance System (NIS) or Folketrygd [2]. In high-income countries, a large proportion of the Gross Domestic Product (GDP) is spent on health. For example, according to the Organisation for Economic Co-operation and Development (OECD), in 2019 the US spent approximately 17.0% of its GDP on health, Germany 11.7%, Japan 11.1%, UK 10.3%, Canada 10.8%, and Australia 9.3% [3]. In most countries, this rate has been increasing in recent decades, and it is expected that there will be substantial pressure for this trend to continue.

There are many reasons for this increase in spending on health, including technological developments (e.g., new treatments, interventions, and diagnostics), demographic changes (e.g., ageing populations), increases in income across populations, therefore increasing demand and expectations from patients/populations, and epidemiological changes such as those related to risk factors for chronic diseases (e.g., increasing prevalence of obesity).

In addition to pressure on health budgets, governments are also under constant pressure to increase funding across multiple areas such as welfare, education, defence, and infrastructure. However, as governments do not have bottomless buckets of money, choices must be made. In the health field, these choices aim to maximise health for the population. When making decisions, trade-offs are made with the aim of reducing any losses associated with the choice that is made. We face such decisions everyday: if I buy the latest, most advanced phone on the market, that means I won't be able to afford the fitness watch that I really want (now!) for a few months. If I bought a middle of the range phone instead, I could afford the fitness watch now. In economics this is referred to as the opportunity cost: the loss (or the benefit) that I would have experienced if I selected one choice instead of the other. Governments aim to make decisions that reduce opportunity costs. In the health field, this is where health economics plays a critically important role. Health economic evaluations provide information upon which evidence-based decisions that incorporate these issues can be made by governments. Quality of life plays an important role in many such evaluations.

14.3 Quality of Life and Health Economic Evaluations

One of the most useful and therefore popular forms of health economic evaluations are cost-effectiveness evaluations and a sub-type referred to as a cost-utility analysis (CUA). This form of evaluation assesses whether the extra cost of a new treatment is justified in terms of the health gains and incorporates a measure of quality of life. CUAs will be the focus of this chapter.

A CUA compares the costs and outcomes of two (or more) treatments. From the perspective of a government payer (e.g., the health department), costs include all relevant costs that would be incurred by government if the new treatment was funded. This can include the drug itself, related hospital costs, along with cost savings, such as reduced length of stay in a hospital.

The outcomes of a CUA are a combination of both the quality and quantity of life. The most commonly used metric to report this is the quality-adjusted life year [4]. The *quantity* of life associated with a treatment is estimated by measuring the associated survival, and *quality* of life is measured using health state utility values (see also Chap. 14, this volume). Health state utility values are a metric of quality of life, and measured on a scale of 0 to 1, with 0 representing death and 1 optimal health. Negative scores representing states worse than death are possible in some instances. Health state utilities can be measured using either direct or indirect methods. An overview of the most commonly used methods is presented below.

14.4 Direct Methods

14.4.1 Standard Gamble

The standard gamble is an approach used to generate health state utility values, in which participants are asked to choose between two options. Figure 14.1 provides an illustration of this approach. Option A is a certain scenario, such as being in a given health state (e.g., chronic kidney disease) for a defined number of years. Option B is a risky option that includes either living in a state of full health for a defined number of years or immediate death. The probabilities of the two states in Option B are altered until the participant values Options A and B equally [4]. If, for example, this point is reached with a probability of death of 85%, this implies that the health condition in Option A is valued at 85% of a state of full health. In turn, a health state utility value of 0.85 would be applied to the health state in Option A.

14.4.2 Time Trade-Off

The time trade-off method was developed by Torrance and colleagues [5] with the aim of eliciting the time that participants are willing to trade-off for quality and quantity of life. Whilst this method provides similar results to the standard gamble technique, it was developed as it was considered easier to administer [6]. In hypothetical scenarios, participants are asked how many of their remaining years of life in a given health state (e.g., asthma) they would be willing to forgo to live in a health state free of disease and/or disability (Fig. 14.2). The underpinning assumption is that the greater the amount of time a participant is prepared to give up, the more substantial is the health burden associated with the disease included in the hypothetical scenario [6, 7]. For example, participants are provided with a hypothetical scenario that they have 10 years of life remaining, with type 2 diabetes requiring insulin injection three times daily, and then at the end of the 10 years they will die without pain or discomfort. Participants will then be asked how many of those 10 years they would be willing to give up, in order to live in optimal/full health, and to then die without pain or discomfort. In this example, we'll assume that participants would be willing to give up 2.5 years, therefore living 7.5 years in optimal health. Based on this, the assumption then follows that the type 2 diabetes health state specified in the scenario (represented by h_d in Fig. 14.2) has 75% of the health state utility of the optimal health state, therefore a health state utility value of 0.75.

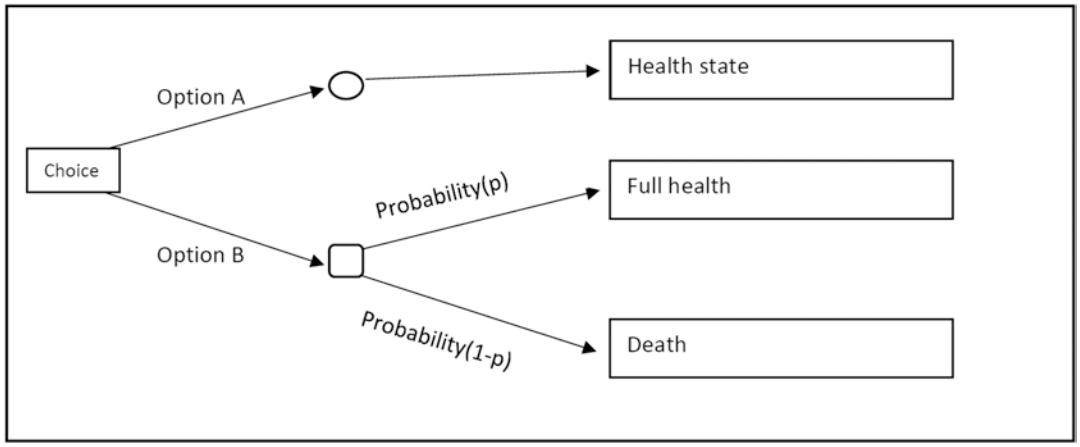

Fig. 14.1 Standard Gamble illustrating chronic health state preferred to death. (Adapted with permission of Oxford Publishing Limited through PLSclear)

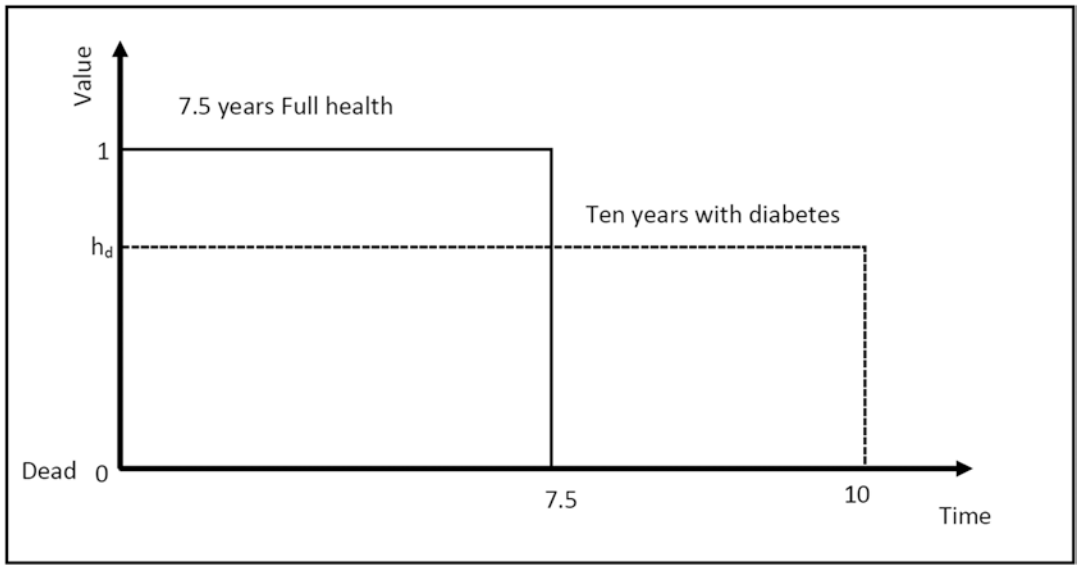

Fig. 14.2 Time trade-off for diabetes type 2 preferred to death

14.5 Indirect Methods

14.5.1 Multi-attribute Utility Instruments (MAUIs)

Both the standard gamble and time trade-off approaches are time-intensive and require participants to understand somewhat complex scenarios and probabilities. Indirect methods of eliciting health state utility values using multi-attribute utility instruments (MAUIs) provide a more straightforward and faster approach to measuring health state utilities.

The indirect approach involves use of pre-scored multi-attribute health status classification systems [4]. A range of MAUI questionnaires have been developed and validated, including the EuroQol-5D (EQ-5D) instruments [8], the Assessment of Quality of Life (AQOL) instruments [9], the Health Utilities Index (HUI) [10], and the Short Form 6D (SF-6D) [11]. Participants complete the questionnaire, and a health state

utility value is then attributed based on a predetermined set of health state utilities, called 'value sets' for the specific MAUI used. As health states can be valued differently based on a range of cultural and social factors, country-specific value sets have been developed for many instruments.

One of the most commonly used MAUIs are the EQ-5D instruments. Three instruments have been developed [12–14], but for the purposes of this chapter, we will focus on the more recently developed EQ-5D-5L. This instrument has five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, and these dimensions are measured on five levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. The instrument has 3125 possible health states [15] and takes less than one minute to complete with just five questions. The instrument is available in more than 130 languages with 22 value sets published to-date [16]. For the US, the minimum health state utility value is −0.573, representing extreme problems across all dimensions, and the highest value is 1.000 [17].

The SF-6D is based on the widely used Short Form 36 (SF-36) quality of life questionnaire. As the SF-36 measures the amount of limitation experienced by a patient, it cannot be directly used to elicit utility values. Instead, an algorithm is applied to 11 items of the instrument, representing 6 dimensions: physical functioning, role limitation, social functioning, pain, mental functioning, and vitality. An algorithm is applied to the participant responses to these items, which was developed based on standard gamble utility measurements from a random sample of the UK population. In turn, this generates health state utility values. The range of potential values generated from this instrument is −0.98 to 1.00 for the UK population [18].

A suite of MAUIs have been developed under the banner of The Assessment of Quality of Life (AQoL) instrument: AQoL 4D, 6D, 7D, and 8D. The most comprehensive of these is the AQoL-8D, which is one of the few instruments with high sensitivity in the psychosocial dimensions of health [15]. The instrument consists of 35 questions and takes approximately 6 minutes to administer [19]. Reflecting the relative length of this MAUI, the AQoL-8D has the largest number of possible health states: 2.4×10^{23}. The range of scores is −0.04 (health states worse than death) to 1.00 (full health).

14.6 Quality-Adjusted Life Years (QALYs)

As mentioned earlier in this chapter, health state utility values are used in combination with a measure of quantity of life (e.g., life expectancy) to generate QALYs – a summary measure of the effectiveness of an intervention. In this way, quality of life, measured through health state utility values, is included in the measure of effectiveness. Use of generic MAUI instruments rather than disease-specific instruments allows for health state utility values, and therefore QALYs, to be compared across different disease areas.

Figure 14.3 illustrates QALYs (i.e., the effectiveness of an intervention). Let us assume we are interested in assessing the effectiveness of a hypothetical new intervention for hepatocellular carcinoma. The y axis shows the health state utility values associated with each intervention, and the x axis shows time in years. The health state utility values are plotted for both the standard treatment and the new treatment.

We can see that all patients start off with the same health state utility value of 0.7. Now, for patients receiving the standard treatment, their health state utility value decreases at 6 months to 0.4. This may be related to side effects of treatment or worsening of the underlying health state. The health state utility value remains stable for the subsequent 6 months and then decreases again at 1 year to just 0.19 – a poor state of health and quality of life. These patients continue at this level for the following 12 months, then the health state utility decreases to 0 at 2 years, indicating death or a state equivalent to it.

Now let us look at the patients receiving the new treatment. Similar to the patients receiving the standard treatment, they start with a health state utility value of 0.7. With this new treatment,

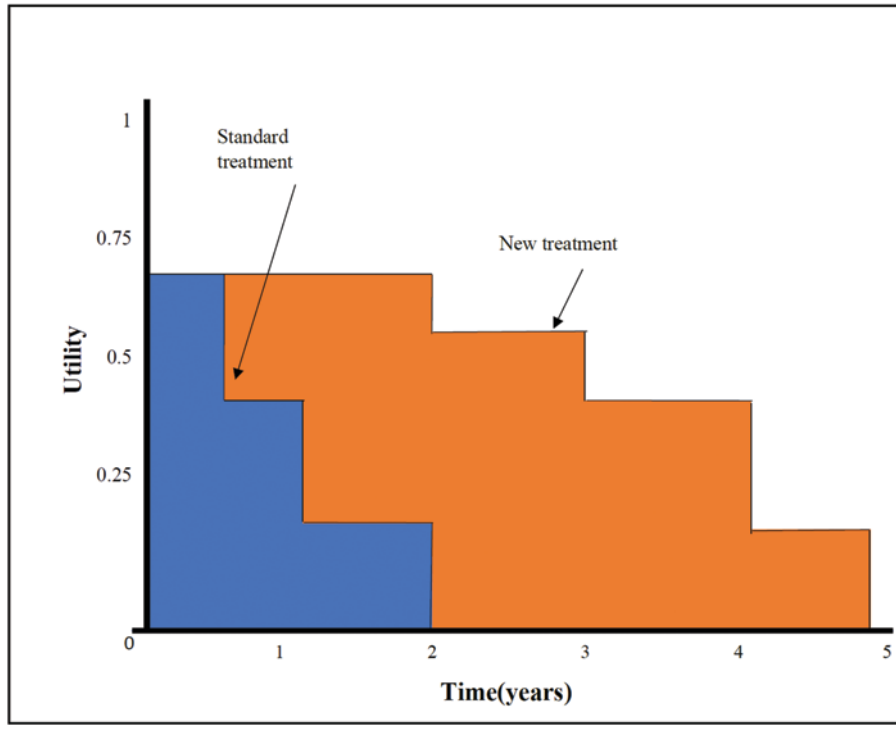

Fig. 14.3 Quality-Adjusted Life Years

they are able to maintain this level for 2 years. This may suggest few side effects and no substantial worsening of their underlying health state and quality of life. At 2 years, the health state utility of these patients decreases to 0.56 and remains at this level for 12 months. At 3 years, a further decrease in utility occurs (to 0.4), and at 4 years, a more dramatic utility decrease to 0.2 occurs. At 5 years, utility decreases to 0, suggesting death or a state equivalent to it. What we are interested in is measuring the difference between these groups, i.e., the QALY gain represented here by the area shaded in orange. Let us now look at how we calculate the QALYs.

14.6.1 Calculating QALYs

QALYs are calculated by multiplying the health state utility value(s) by the number of years spent in the health state(s). So, one year of life lived in perfect health (i.e., utility of 1) is worth 1 QALY. One year of life spent with a utility value of 0.75 is worth 0.75 QALYs.

Let us apply this to our scenario comparing the hypothetical new treatment for hepatocellular carcinoma with the standard treatment. For the standard treatment, we have:

- 6 months with a health state utility of 0.7;
- followed by 6 months with a health state utility of 0.4;
- and then 1 year with a health state utility of 0.19.

We calculate this as: $(0.5 \times 0.7) + (0.5 \times 0.4) + (1 \times 0.19)$.

Therefore, this treatment is associated with 0.74 QALYs.

Now let us look at the new treatment. We have:

- 2 years with a health state utility of 0.7;
- followed by 1 year with a health state utility of 0.56;
- then 1 year with a health state utility of 0.4;
- and 1 year with a health state utility of 0.2.

We calculate this as: $(2 \times 0.7) + (1 \times 0.56) + (1 \times 0.4) + (1 \times 0.2)$

Therefore, the new treatment is associated with 2.56 QALYs.

By subtracting the QALYs of the new treatment from the standard treatment $(2.56 - 0.74)$, we can see that the new treatment is more effective, with a gain of 1.82 QALYs. Whilst this is an excellent improvement regarding QALYs for patients, we must also consider the costs of these treatments.

14.7 Incremental Cost-Effectiveness Ratio (ICER)

To compare both the costs and effectiveness (i.e., QALYs), we will calculate a straightforward ratio, called the incremental cost-effectiveness ratio (ICER). This provides a measure of the cost-effectiveness of an intervention, with the ICER representing the average incremental cost of one additional unit of the measure of effect, that is, our new treatment for hepatocellular carcinoma.

The formula for this is:

$$\text{ICER} = \frac{\$_{\text{new treatment}} - \$_{\text{standard treatment}}}{\text{Effectiveness}_{\text{new treatment}} - \text{Effectiveness}_{\text{standard treatment}}}$$

For our hepatocellular carcinoma scenario, we will assume that the standard care, in total, costs $40,000 per patient. The new treatment costs a lot more, at $100,000 per patient. So, we will follow the formula above.

$$\text{ICER} = \frac{\$100{,}000 - \$40{,}000}{2.56\,\text{QALYs} - 0.74\,\text{QALYs}}$$

Therefore, our ICER is $32,967 per QALY gained. But what does this mean?

14.8 Willingness to Pay

We now need to put the ICER into context, so we can understand what this result means. In health economics, we use a 'willingness-to–pay' threshold, a point at which a new intervention is considered to be good value for money [20]. These thresholds have been developed to incorporate considerations of the value of leisure time, quality of life, life expectancy, and non-health consumption [20]. The threshold is an estimate of the theoretical estimate of what an individual would be willing to pay to extend their life in full health by 1 year. Willingness-to-pay thresholds are commonly estimated using a country's GDP [21]. According to the WHO's *Choosing Interventions that are Cost Effective* project, an intervention with costs less than three times a country's GDP per capita is considered cost-effective and less than one time the GDP per capita is very cost-effective. There are several limitations to this approach: in response, several other methods have been developed to improve this metric. Whilst an in-depth discussion of this is not relevant to this chapter, further reading on this topic is suggested in the Further Reading section [20–22].

Willingness-to-pay thresholds can be implicit or explicit. In the UK, the National Institute for Health and Care Excellence (NICE) uses a threshold of between £20,000 and £30,000 per QALY for reimbursement through the NHS [23], thresholds between USD$50,000 and USD$100,000 are cited for the US [24], CAD$20,000–$100,000 in Canada [25] and AUD$50,000 in Australia, within a range of AUD$45,000–$60,000 [26, 27].

For our scenario looking at a new treatment for hepatocellular carcinoma, we calculated an ICER of $32,967 per QALY gained. We did not specify a currency for which this was calculated, but looking at the willingness-to-pay thresholds above, we will assume that this new treatment will be cost-effective in many high-income settings.

It is important to note that not all treatments that are subsidised fall within a willingness-to-pay threshold. At the beginning of this chapter, we mentioned that many of the new cancer therapies are very costly. The OECD notes that the development of high-cost drugs (including cancer drugs) over recent years will continue to be a major driver of increased health expenditure in the future [28]. Whilst some of these new drugs have provided cures for cancer, others provide much more marginal benefits, such as increased survival of 2–3 months. For a patient or family member, an extra 3 months of life may be highly desirable. However, as governments and insurers do not have a bottomless bucket of money, financial sustainability is an essential component of decision-making.

Orphan drugs for very rare diseases, including some cancers, are an example of these high-cost drugs. Some health economists argue that orphan drugs to not provide good value for money, and when governments subsidise these, the opportunity cost is a sacrifice in the overall health of the population [29]. Others argue that in the absence of effective treatments for rare, life-threatening conditions, the high cost of these drugs is justified. Irrespective, many governments are providing subsidised access to these high-cost drugs.

14.9 Conclusion

Cost-effectiveness evidence plays an important role in decisions to fund clinically effective cancer therapies. Importantly, many funding bodies require cost-effectiveness evidence that incorporates a measure of quality of life, i.e., the QALY. This allows for quantification of both the quantity and quality of life associated with a new therapy in comparison to that associated with existing therapies.

Over recent years, high-cost cancer therapies have become increasingly available (and subsidised), despite the ICERs being well above the willingness-to-pay threshold. This occurs in the context of life-saving therapies and also for those which only offer marginal benefits to patients. As these high-cost drugs will continue to be a driver of increased health expenditure in future years, it is of critical importance to consider the opportunity costs of these decisions in the context of the wider health financing system.

14.10 Questions That Can Be Used for Learning/Teaching

Q1 A person lives for 6 years with disease A. They use the standard treatment to manage this condition. Treatment of disease A is associated with a health state utility value of 0.5. Calculate how many QALYs this person has.

A. 6 years × 0.5 utility = 3.0 QALYs over the 6 years.

Q2 A new treatment has become available for disease A. This new treatment is associated with an improved health state utility of 0.75. Calculate the QALYs over the 5 years if the person uses the new treatment.

A. 6 years × 0.75 utility = 4.5 QALYs over the 6 years.

Q3 What is the QALY gain associated with this new treatment?

A. 4.5 QALYs −3.0 QALYs = 1.5 QALYs gained over 6 years from the new treatment.

Q4 The cost for the standard treatment over 6 years for this patient is $150,000. This includes prescription medications and 6-monthly MRIs. The new treatment costs $400,000 over 6 years, which mainly consist of fortnightly infusions of the new treatment and 3-monthly MRIs. Calculate the ICER for this new treatment.

$$\text{ICER} = \frac{\$_{\text{new treatment}} - \$_{\text{standard treatment}}}{\text{Effectiveness}_{\text{new treatment}} - \text{Effectiveness}_{\text{standard treatment}}}$$

$$= \frac{\$400,000 - \$150,000}{4.5\,\text{QALYs} - 3.0\,\text{QALYs}}$$

$$= \$166,667 \text{ per QALY gained.}$$

Q5 Does this ICER fall within the willingness-to-pay threshold for your country?

A. Look up the GDP per capita for your country. If the ICER is less than three times the GDP per capita, you can consider this new treatment to be cost-effective.

Q6 If the ICER is above the willingness-to-pay threshold, what sort of information would you require to help you to decide whether this treatment should still be considered for reimbursement?

A. You would want to know more about the condition including the severity of it, incidence, prevalence, and survival. In addition, you would want to know if there are any other treatments available, and how effective they are.

14.11 A Topic for Discussion That Can Be Used for Teaching

Below is a scenario which you are asked to read. You will then need to decide how to use the resource (money in this case) you have to meet the requests. Remember, ALL healthcare systems have financial constraints. There is no consensus regarding a fair way in which to decide on which intervention(s) to fund.

Scenario:

Whilst conducting the end of financial year account summary, the manager of the government health organisation has discovered there is an extra $100,000 left in the budget. If this money is not spent, it will be lost in the new financial year. The manager invites heads of departments to submit requests.

The four requests are:

Option 1:

The patient concerned is a working mother aged 41 years with two children aged 10 and 6 years. Her husband died 5 years ago from prostate cancer. She has bravely fought her brain tumour, but it has recurred after standard therapy and the doctors are now saying the only hope is treatment with a new drug. This drug is undergoing clinical trials, so it is not yet available through government subsidy. As a result, the treatment is expensive, costing $70,000 per year, which the patient is unable to afford. As the drug is still under investigation, the effectiveness is unknown.

Option 2:

Five children between the ages of 3 and 12 years are waiting to receive a new antiepileptic drug. The children come from mixed family backgrounds, but all are finding that their quality of life is affected by their epilepsy; in particular, their educational achievement is suffering. The cost of providing the newer drug to all five children for a year is $15,000 and the expected gain in quality-adjusted life years (QALYs) is estimated to be 0.05 per annum.

Option 3:

A patient has been on the waiting list for bariatric surgery (gastric bypass) for 9 years. Over this period, he has gained more weight, is experiencing severe osteoarthritis related to obesity, and has developed Type 2 diabetes. The cost of the surgery is $76,000, and it is known to be the most effective intervention for weight loss. It is also possible his osteoarthritis and diabetes may be improved if significant weight loss is achieved. The estimated QALY gain from this surgery 0.9.

Option 4:

A male patient aged 87 years is suffering from motor neurone disease, a progressive degenerating disease leading to impaired speech, swallowing, and breathing. There is no cure for the condition but quality of life can be improved for the short period of life remaining by taking drug A. The patient desperately wants to be able to attend his granddaughter's wedding in three weeks' time in a reasonable health state which he believes this drug will help him achieve. The financial cost is $30,000 and the expected benefits are 0.09 QALYs.

You have been asked to look through these options and come up with a recommendation. Consider the costs, number of patients, the QALY gains, age, ethical considerations, and opportunity cost. Think about whether you have any personal biases that influence your decision-making.

There is no correct answer.

14.12 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

- Drummond, M., et al., Methods for the Economic Evaluation of Health Care Programmes, 3rd edition. 2005, Oxford: Oxford University Press.
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14.13 Research in Context

This paper* compares cost-utility analyses conducted in the UK and the US for cancer drugs. In the UK, the National Institute for Health and Care Excellence (NICE) assesses the clinical and cost-effectiveness of new treatments, and issues recommendations to the National Health Service for public coverage. In contrast, nobody in the US has a formal role in reviewing evidence and recommending provision of new treatments. In 2006, a non-government, independent institute was formed – the Institute for Clinical and Economic Review (ICER) – with the aim of increasing transparency in decision-making between drug makers and insurers.

The authors of the paper note that whilst the methodology used in cost-utility analyses is relatively standardised, funding decisions can vary tremendously depending on the context. Health financing systems, reimbursement processes, and drug price negotiation all play important roles and vary by country. The paper clearly articulates the important role NICE plays in achieving lower prices for new drugs through the use of cost-utility analyses and value-based pricing.

* Cherla A, Renwick M, Jha A, Mossialos, E. Cost-effectiveness of cancer drugs: Comparative analysis of the United States and England. E-Clinical Medicine 2020;29–30:100625. doi: https://doi.org/10.1016/j.eclinm.2020.100625 [published Online First: 2021/01/14]

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Satisfaction with Cancer Care

15

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Contents

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15.1 Introduction

In most Western countries, the assessment of satisfaction with care is now considered an important indicator for quality of care. Initially encouraged by funding agencies and patient groups, this assessment is now required by healthcare accreditation bodies as part of programmes to monitor and improve the quality of care. It enables hospitals to be compared and benchmarked, that is to identify the best performing structures that can serve as a model for others. Measuring patient satisfaction should thus make it possible to better meet their needs and expectations. It also contributes to it because satisfaction or dissatis-

A. Kassianos (ed.), *Handbook of Quality of Life in Cancer*, https://doi.org/10.1007/978-3-030-84702-9_15

faction with care can influence patient behaviour and thus affect patient outcomes. Several studies have indeed shown the effect of satisfaction on seeking care (e.g., doing what needs to be done to receive care, changing one's lifestyle, adhering to therapeutic programmes, adhering to medical follow-up, referring to recommended caregivers or services) and on the patient's reactions to care services (e.g., recommending a service, changing care institutions, writing a letter of complaint) [1]. The link between satisfaction with care and adherence to medical advice would in fact be largely determined by the quality of caregiver-to-patient communication [2]. Good caregiver-to-patient communication is also likely to promote satisfaction [3], adherence, and continuity of care. It would thus contribute to the overall improvement of the patient's health status.

The evaluation of patient satisfaction is therefore particularly important in oncology [4]. Patients with cancer typically experience discomfort from the side effects of mid- to long-term treatments, uncertainty about the nature, course and prognosis of their condition, reduced ability to control their own lives, increased dependency on others, and disruption to their family, work, and social lives [5]. The evolution of diagnostic procedures, therapeutic programmes, and the provision of supportive or rehabilitative care require an ongoing assessment of patient satisfaction with complex multidisciplinary care and services. In this context, and particularly when treatments no longer have a curative aim, the therapeutic objective can no longer be limited to biomedical variables alone, such as prolongation of survival or response rate to treatment, but should also target quality of life, which also affects patient satisfaction [6, 7].

The present chapter addresses the theoretical models currently proposed to understand what patients mean in rating their satisfaction with the care. The following sections of this chapter bear on the rationale and purposes of patient satisfaction assessment. Then, examples of patient satisfaction assessments and study results within the context of clinical research and health care quality evaluation in oncology are provided.

This chapter will enable readers to (a) understand the definition and specificities of satisfaction with care in the context of cancer care; (b) examine existing tools to evaluate satisfaction; and (c) have an insight into the current state of research on determinants of satisfaction with oncology care.

15.2 The Satisfaction with Care Concept and Its Dimensions

Assessing satisfaction with care faces a number of conceptual issues. The needs of patients in the context of care are manifold. Of particular note is the significant dependence of patients on caregivers. Several questions arise: "what does it mean to be satisfied with care, what is the role of expectations, values, reality of care on satisfaction with care, what are the aspects of care that mainly lead to patient satisfaction?". Identifying the factors that influence patient satisfaction makes it easier to interpret this assessment. These may be patient-related factors (e.g., age, education, cultural background, health status), which then identify groups of patients at risk of less favourable care experiences (e.g., elderly patients, patients with psychiatric disorders) or factors related to the structure or process of care, which are then identified as aspects of care to be improved (e.g., type or number of professionals, scope of services offered, continuity of care).

With regard to the term "satisfaction", the dictionary provides the following definitions: "satisfaction" defines "the action of satisfying a claim, a need, a desire" and "contentment, a pleasure that results from the accomplishment of what one expects, what one desires". Thus, if the patient feels that he or she is receiving what he or she wants, based on his or her needs and desires for care, satisfaction will be high. However, everyday language also uses the word "satisfying", meaning sufficient, and implying the achievement of a minimum standard. The term "satisfaction", corresponding both to a complete and to a minimum sufficient response to needs, is therefore ambiguous. This complicates the interpretation of answers to satisfaction questionnaires in relation to care.

Satisfaction is related to patient-specific factors. Patients have a set of characteristics (e.g.,

age, gender, education, personality), personal values, and prior experiences. These, combined with the knowledge and information they acquire through contact with care, enable them to define their situation and determine their needs for care, and thus, gradually form a set of expectations regarding the results of their care, the attitude of caregivers, and the performance of the system. They form the standard against which received care will be evaluated and judged satisfactory or unsatisfactory. These expectations however are subject to many changes over the course of illness and treatment.

Early theories of patient satisfaction defined this concept as an assessment of how well patients' expectations of care were met. This definition has been questioned in recent years in the face of systematic observations of high levels of satisfaction in surveys. Few patients are critical of the care they receive. Williams et al. [8] suggest that a patient's expression of dissatisfaction with a negative experience of care reflects the perception of "unfulfilled duty (of care providers or care services)". Satisfaction would mean: "they are doing the best they can with the means at their disposal" or "it is not quite their job to (meet some type of unmet need)...". The scores obtained from satisfaction questionnaires would therefore not allow for the identification of gaps in care and care services in relation to patient needs.

The issue with systematically high scores in care satisfaction questionnaires can be circumvented by developing more refined and rigorous investigative methods [9]. Thus, it appears that evaluating specific and detailed aspects of care provides more diversified satisfaction scores. In this regard, a growing consensus has emerged around a multidimensional conception of satisfaction [1, 4, 10, 11]. It has been found that different characteristics of caregivers and care influence satisfaction; similarly, patients develop distinct opinions about each of these characteristics. Table 15.1 presents a taxonomy of the concept of satisfaction with care, based on studies on general populations [1]. This author has attempted to clarify the nature and number of dimensions of the concept of satisfaction.

Interpersonal aspects of care are generally considered to be an essential dimension of satisfaction [9]. These include communication skills, empathy, and reassurance. They also include the balance of control in the caregiver-patient relationship, non-verbal aspects of communication (e.g., body position, head position, and eye contact), and personal characteristics of the caregiver such as kindness or sympathy. With regard to the technical aspects of care, various authors have expressed doubts about patients' ability to judge the technical skills of caregivers. Some have

Table 15.1 Satisfaction with care: dimensions, definitions and examples [85]

Dimensions	Definitions	Examples
Technical skills	Caregivers' skills and adherence to optimized standards of diagnosis and treatment	Timeliness, accuracy, risk, and error mitigation
Interpersonal skills	Characteristics of personal communication between caregivers and patients	Attention, kindness, courtesy, respect
Effectiveness results	Care outcomes	Ability to improve or maintain health
Financial aspects	Factors involved in paying for care	Cost of care
Accessibility-comfort	Factors involved in obtaining care	Waiting time in the waiting room, distance of residence from the care institution
Availability	Presence of care resources	Adequate number of hospitals and caregivers for a given geographical area
Environment	Physical aspects of the place of care	Cleanliness
Continuity	Coverage by the same carer and/or the same place of care	Knowing one's referent doctor

Source: Adapted (translated) from Delvaux N, Brédart A, Libert Y, Merckaert I, Liénard A, Delevallez F, Hertay A, Razavi D. Chapter 12 - Communication soignant-soigné: problématiques. In: Razavi D, Delvaux N, editors. *Psycho-oncologie: concepts théoriques et interventions cliniques, 2nd Edition*. Issy-les-Moulineaux: Elsevier Masson SAS. p. 395–430. Copyright 2019, with permission from Elsevier. https://doi.org/10.1016/B978-2-294-75811-9.00012-X

mentioned the danger that this judgement may be based, for example, on the attractiveness of technical interventions. However, several studies have shown that the views of patients and caregivers on the quality of care can converge [12]. This aspect should therefore be taken into account when assessing satisfaction with care.

A study carried out in Australia with patients in outpatient treatment showed the importance given by patients to the technical competence of the doctor, his relational and communicative qualities, accessibility and continuity of care, hospital care, clinics, non-medical care, contact with the family and financial aspects [5]. Among the aspects mentioned, greater importance is attributed to the technical quality of medical care, the relational and communicative qualities of doctors, and accessibility to care.

15.3 Evaluation

15.3.1 Objectives of the Evaluation

Satisfaction with care can be assessed at different levels, whether in a research, clinical practice or hospital setting: first, at the level of a medical examination, treatment (e.g., medication or surgical procedure), or psychosocial intervention (e.g., psychotherapy, type of psychology training); second, at the level of a model of care organization for a particular group of patients (e.g., organization of palliative care); third, at the level of a service (e.g., day hospital); fourth, at the level of a healthcare system. These assessments can provide results in terms of the acceptability or preference of a treatment or intervention, identification of sources of dissatisfaction with care or reasons for non-compliance with treatment, and can provide data for benchmarking. Based on these study results, optimal treatments can be recommended or priorities can be set among choices of quality-of-care improvement initiatives. Quality improvement interventions implemented at the level of processes, services, or organization of care can then be evaluated over time using the same patient satisfaction assessment tools. Box 15.1 lists the objectives of assessing satisfaction with care.

Box 15.1: Satisfaction with Care: Evaluation Objectives [85]

Domains
- Clinical research (e.g., screening, treatment, care, psychosocial support).
- Clinical practice (e.g., consultation, examination).
- Hospital management (e.g., institutional care organization).
- Evaluation of healthcare systems (e.g., care provided at a national level).

Expected results
- Determine the optimal treatment in terms of acceptability or preference.
- Identify sources of dissatisfaction.
- Identify the reasons for non-acceptance, non-compliance with the proposed treatment.
- Develop databases for benchmarking.

Decisions
- Implement the best treatment.
- List priorities in terms of investment of resources.
- Implement and monitor the impact of innovative or alternative interventions, care programmes, services, or organizations.

Source: Adapted (translated) from Delvaux N, Brédart A, Libert Y, Merckaert I, Liénard A, Delevallez F, Hertay A, Razavi D. Chapter 12 - Communication soignant-soigné: problématiques. In: Razavi D, Delvaux N, editors. *Psycho-oncologie: concepts théoriques et interventions cliniques, 2nd Edition*. Issy-les-Moulineaux: Elsevier Masson SAS. p. 395–430. Copyright 2019, with permission from Elsevier. https://doi.org/10.1016/B978-2-294-75811-9.00012-X

In the context of randomized clinical trials, information on patient satisfaction levels can add a unique perspective to the assessment of treatment effectiveness. On the one hand, this measure can be analysed as a dependent variable, an

index of the effects of treatment on patients' quality of life. Thus, for example, differences in satisfaction may arise when comparing different treatment modalities (e.g., 5 rather than 12 courses of chemotherapy). One might expect that a treatment of 12 courses of chemotherapy would be considered less satisfactory because of the discomfort caused by the accumulation of side effects and the numerous trips to the hospital. However, patients may feel that this type of treatment compared to five courses of chemotherapy provides better results on the tumour and therefore be more satisfied in terms of therapeutic efficacy. On the other hand, satisfaction can be considered as an independent variable that can explain the variability of patients' desire to undertake and continue often heavy and toxic treatments. Thus, it can be expected that the interpersonal qualities of physicians (e.g., letting patients express their complaints and providing information in an understandable manner) are significantly related to the patient's tolerance and compliance with chemotherapy or radiotherapy treatments.

Expectations of care may differ depending on the perspective of patients and physicians. Confronting these perspectives is another way of using and understanding patient satisfaction data to improve patient care. For example, one study shows that oncologists want less involvement in care and treatment choices than patients do; unlike patients, they believe that families receive sufficient explanations about care and treatment [13].

15.3.2 Examples of Assessment Instruments

The use of rigorously developed measures of satisfaction with care can provide information on the quality of care [14]. Care satisfaction questionnaires designed for oncology have been developed for a variety of purposes, including assessing satisfaction with a hospital oncology service [15], an ambulatory radiotherapy service [16], a breast cancer screening service [17], a mammography [18], an outpatient medical consultation [19], or for the evaluation of a treatment [20], a modality of care [21], or a specific intervention such as a structured provision of information [22], a doctor-patient communication facilitating participation in therapeutic decisions [23], or allowing informed consent to be obtained [24]. Table 15.2 provides some examples of satisfaction questionnaires regarding care developed in different contexts of oncology management.

Oberst developed an instrument consisting of five visual analogue scales measuring patients' opinions of the quality of medical and paramedical care in general, the degree of satisfaction with care expectations, and the degree of satisfaction with information about treatment and care [4]. McCusker adapted a satisfaction questionnaire to assess the impact of a new home care programme for chronically and terminally ill patients [29]. The questionnaire is composed of scales covering the following aspects: general satisfaction, availability of care, continuity of care, physician presence, skills, communication skills and personal qualities, patient and family involvement in treatment choices, pain relief, preference for home care over hospital, and physician decision-making regarding treatment choices. Kristjanson developed an instrument to assess family satisfaction with the care of a patient with advanced cancer [30]. This scale has four subscales and is composed of 20 Likert-type items covering aspects of information, availability, physical care, and psychological support. Loeken created a questionnaire on patient satisfaction with the mammography examination (27 items covering the structure of care, e.g., convenience, accessibility, physical environment of the department), the care process (e.g., information, interpersonal and technical skills), physical and psychological discomfort, and general satisfaction (e.g., present, future satisfaction, intention to continue medical follow-up). Loblaw has developed and tested a questionnaire assessing satisfaction with outpatient medical consultations in oncology ("Princess Margaret Hospital Patient Satisfaction with Doctor Questionnaire (PMH/PSQ-MD)") [19], which consists of 29 questions to be answered on a four-point scale. A factor analysis of 174 outpatients confirmed the existence of four areas of medical consul-

Table 15.2 Satisfaction with oncology care: example of multidimensional questionnaires [85]

Care setting	Aspects of care assessed
Medical consultation PMH/PSQ-MD [19]	Information, empathy, interpersonal skills, quality of time
Bedside check-up [25]	Needs considered, active participation, interaction, information, support
Cancer Genetic consultation [26]	Clinician competence, interpersonal skills, waiting time, team attitude
Medical Decision Process [23]	Information given on aspects important to the decision, decision made, alignment of the decision with personal values
Inventory of aspects of the physician-patient relationship PPRI [27]	Attention and professional skills, empathy
Mammography (MGQ) [18]	Discomfort, interpersonal skills, information, technical skills, waiting time
External radiotherapy [16]	Organization, access, waiting time, comfort, information, assistance
Nursing care at chemotherapy day hospital (WCSQ) [21]	Nursing care, patient education, environment, availability of medical and healthcare team, hospital accessibility
Chemotherapy day hospital [4]	Meeting expectations, medical care, nursing care, information
Outpatient oncology consultation [28]	Ease of access, waiting times, support, continuity, discharge information
Palliative home care service [29]	Availability, continuity, communication, interpersonal skills, preferences, participation in medical decisions, pain relief
Family satisfaction with advanced cancer care (FAMCARE Scale) [30]	Information, availability, patient care, pain relief
Generic questionnaire on satisfaction with care (CASC and EORTC PATSAT33) [31, 32], questionnaire specific to inpatient (EORTC IN-PATSAT32) [33] and outpatient (EORTC OUT-PATSAT7) care [31, 32]	Technical skills, interpersonal skills, information, availability, organization of care, and services
Arrangements for medical surveillance after cancer treatment (34]	Length of hospitalization, preference, wish to recommend, home care
Patient satisfaction with interpersonal relationship with navigator (PSN-I) [35]	Patient satisfaction with the relationship with a navigator

Source: Adapted (translated) from Delvaux N, Brédart A, Libert Y, Merckaert I, Liénard A, Delevallez F, Hertay A, Razavi D. Chapter 12 - Communication soignant-soigné: problématiques. In: Razavi D, Delvaux N, editors. *Psycho-oncologie: concepts théoriques et interventions cliniques, 2nd Edition*. Issy-les-Moulineaux: Elsevier Masson SAS. p. 395–430. Copyright 2019, with permission from Elsevier. https://doi.org/10.1016/B978-2-294-75811-9.00012-X

tation, assessed by this questionnaire: information exchange, interpersonal skills, empathy, and quality of time spent in consultation. Sitzia has developed an instrument to assess patient satisfaction with outpatient chemotherapy treatment ("Worthing Chemotherapy Satisfaction Questionnaire (WCSQ)") [21]. Six aspects of care are measured by this instrument: interpersonal aspects, technical aspects of care, patient education, multidisciplinary work of the care team, care environment, and hospital accessibility. Twenty-seven items are about the subjective perception of satisfaction.

Brédart developed and tested a 61-item instrument on satisfaction with cancer care in several European countries: the "Comprehensive Assessment of Satisfaction with Care (CASC)" [36–38]. The psychometric analyses of this questionnaire translated into 12 languages resulted in the "EORTC IN-PATSAT32"questionnaire specific to the evaluation of inpatient management for cancer treatment, validated in an international study within the framework of the Quality of Life Study Group of the European Organization for Research and Treatment of Cancer (EORTC) [33] (see also Chap. 5, this volume). This questionnaire focuses on the technical, interpersonal, and communication skills and availability of doctors and nurses and on specific

aspects of care that are important in the context of oncology: the qualities of the technical, reception, and laboratory staff, the exchange of information between caregivers, waiting times for the results of medical examinations or the initiation of treatment, accessibility, the hospital environment, and overall satisfaction. This questionnaire was able to demonstrate its psychometric performance and its ability to clearly distinguish between groups of patients according to their wish or unwillingness to recommend their hospital or the degree to which they were affected by the side effects of treatment. The "EORTC IN-PATSAT32"questionnaire was then validated in several other European and Asian countries demonstrating favourable psychometric properties, but its full study remains to be continued, particularly to determine the meaning for the patient of a difference in score [39].

With advances in oncology treatments and management methods, this questionnaire has been updated. This allows a more extensive application of this questionnaire to outpatient care and the comparison of management modalities. A generic questionnaire, regardless of the type of treatment, and a module specific to outpatient care have been developed from this revision. Psychometric validation at an international level is currently under way within the European Organisation for Research and Treatment of Cancer Quality of Life Group [31, 32].

As care processes evolve, instruments measuring patients' perceived satisfaction with care constantly need to adapt to renewed issues. Several recent studies have underlined the need for further research on refining satisfaction assessment instruments encompassing comprehensive dimensions of patient-centred care and on improving their psychometric properties [39–41].

15.4 Research on Satisfaction with Cancer Care Determinants

Research on satisfaction with care thus developed from the 1970s onwards, in the context of various medical specialties (e.g., general medicine, mental health, paediatrics, dentistry). Table 15.3 reports socio-demographic, institutional, and clinical factors for which a relationship with patient satisfaction with oncology care has been established. Cancer patient satisfaction may also vary according to other factors such as the psy-

Table 15.3 Satisfaction with oncology care: associated factors [85]

Socio-demographic characteristics	
Age	Younger (<50), less satisfaction [42]
Level of education	Higher education, less satisfaction [43]
Travel to the hospital	Longer commutes to hospital, less satisfaction [43]
Characteristics of the hospital	
Staff (number of doctors/nurses/radiation therapy technicians per bed or machine)	More nurses, more satisfaction [44]
Size of hospital/ department	Smaller size, more satisfaction [44]
Psychological factors	
Personality	No significant association with satisfaction for most personality factors [48]
Coping styles and mental attitudes to disease	Non-consistent relationship between lucid confrontation with the disease, active search of medical information, less satisfaction [13, 45–47]
Presence of psychopathological comorbidities	Anxiety and/or depression, less satisfaction [48–50]
Quality of patient-clinician relationship	Better communication, better satisfaction [3, 46, 51, 52]
Perceived curability of disease	Perceived curability, better satisfaction [53]
Clinical features	
Treatment toxicity	More toxicities, less satisfaction [44]
Symptoms and physical, emotional, social functioning	Better functioning, fewer symptoms, more satisfaction [6, 44, 54, 55]

Source: Adapted (translated) from Delvaux N, Brédart A, Libert Y, Merckaert I, Liénard A, Delevallez F, Hertay A, Razavi D. Chapter 12 - Communication soignant-soigné: problématiques. In: Razavi D, Delvaux N, editors. Psycho-oncologie: concepts théoriques et interventions cliniques, 2nd Edition. Issy-les-Moulineaux: Elsevier Masson SAS. p. 395–430. Copyright 2019, with permission from Elsevier. https://doi.org/10.1016/B978-2-294-75811-9.00012-X

chological or cultural background or innovative management modalities. This would benefit from being further studied to improve oncology care.

In addition, patients' opinion was shown to be influenced by care factors. However, this judgement is subjective and may be influenced by patients' personal characteristics, preferences, expectations, or personality type. For example, elderly patients tend to be more satisfied with care [42], while patients with higher levels of education [43] are less satisfied.

A study analysing the relationship between personality factors as measured by the Five-Factor Personality Inventory and patient satisfaction as measured by the Hospital Care Satisfaction Questionnaire found an only marginal contribution from one of the factors, that of "wanting to be pleasant" (e.g., accepting others as they are) [56].

Different coping styles, although not related to other personal and disease characteristics, have been shown to influence patients' question-asking and participation in decision-making during medical consultations [47]. Study results may be contradictory; however, some patients who cope with the illness confront it lucidly, actively seek medical information, and tend to be less satisfied with care than patients who deny or avoid thinking about the situation [57, 58]. Patients who display higher levels of psychological distress, anxious preoccupations, helplessness, and lower fighting spirit also show lower levels of satisfaction [59].

A significant number of cancer patients may face persistent psychological distress during and after treatment [60–62], with prevalence of depression ranging from 4% to 60% [62–64], depending on treatment modalities, type of cancer and symptom screening method, timing, and location. Higher psychological distress levels in breast cancer patients have been shown to be associated with less satisfaction with care [46, 47], in particular doctor care (doctors' interpersonal skills, availability, and waiting time) [48, 49]. Similarly, elder breast cancer patients showing increasing depressive symptoms tend to express lower satisfaction levels [50].

Lam et al.'s [3] prospective study of Chinese women with breast cancer suggests that unmet health information needs and higher anxiety and depression levels at initial treatment phases are predictors of poorer satisfaction with care. A large multicenter study among 4020 cancer patients in Germany [51] has shown patients who were less satisfied with information received and had more unmet needs reported more anxiety, depression, and lower quality of life. The link between information satisfaction and symptoms of distress was confirmed by a later study [52], which both indicated that a more adapted provision of information would improve symptoms of anxiety and depression and that conversely reducing distress levels would increase satisfaction with received information. According to Costantini et al. [53], while awareness of diagnosis and prognosis does not seem to increase emotional distress or decrease satisfaction with care and information, perceived curability is positively associated with greater satisfaction as well as with better emotional adjustment.

Finally, the quality of the patient-physician relationship partly determines patient satisfaction, level of self-efficacy, and emotional distress [46], confirming general literature on doctor-patient communication and satisfaction with care in oncology [65, 66].

A positive relationship has been found between quality of life and satisfaction with care [36, 38, 67, 68]. However, the meaning of this relationship is difficult to establish. Different hypotheses have been put forward. Because caregivers may react differently to patients' personality or behaviour, they may feel more comfortable with patients with fewer problems, pay more attention to them, and provide better quality of care as a result. But patients may also perceive better quality of care because they have a better quality of life. Quality of life would no longer just reflect the effects of disease and treatment on patients' well-being, but also the way they are managed.

Levels of satisfaction with care are generally high. Reasons for dissatisfaction with the structure of care are the insufficient number of home care structures; difficulty in obtaining medical equipment at home; distance of home from hospital structures; waiting times to see the doctor, to obtain drugs, to receive chemotherapy, to carry

out administrative procedures, to receive pain treatment; poor organization of care (e.g., coordination of care, exchange of information between care providers); the cost of treatment and the possibilities of reimbursement for care; and being followed too often by different doctors.

At the level of the care process, studies show high levels of satisfaction with the technical skills and human qualities of caregivers. However, complaints are expressed by a significant number of patients regarding a poor initial diagnosis of cancer; a long delay before the cancer diagnosis is announced; inadequate information on the diagnosis, on the benefits of treatments and their side effects, on symptom control at home, on clinical trials treatments; a lack of availability from caregivers (e.g., frequency of visits, time allocated to the patient during consultation); a lack of appropriate information and referral to services to help with psychological, social, or financial problems and belated referrals to specialist physicians.

The evaluation of satisfaction with treatment is also increasingly being taken into account in cancer research. For example, the evaluation of two pain treatment modalities includes an assessment of patient satisfaction with symptom relief, side effects, and the method of treatment administration [69]. Similarly, surgical procedures for breast reconstruction after breast cancer treatment also involve patient input, including perceptions of cosmetic results, appearance, surgical procedure, and physical sequelae [70].

In addition, various psychological interventions have been tested in oncology to improve communication with the patient. Information is primarily oral during consultations; it may be supplemented by written materials (e.g., brochures, magazines, memory-aid cards, pre-consultation question lists, personalized medical summaries) [71] or audio-visual (e.g., films, audio-recordings) [72]. These initiatives are complemented by training programmes to improve doctors or caregivers' communication skills [73, 74]. The evaluation of these initiatives focuses not only on retention of provided information but also on patient satisfaction, their perception of the quality of provided information, expressed empathy, listening, interpersonal skills, and the quality of time available to the patient in the setting of care [19, 75]. There are also educational approaches aimed at developing the patient's own communication skills. These include interventions to assist in question formulation or preparation for the consultation with the oncologist, which are also evaluated in terms of patient satisfaction [76, 77].

Information given to patients about their disease and treatments also allows them to take part in treatment decisions. Cancer patients are often confronted with treatment alternatives that have similar therapeutic results but different consequences in terms of side effects, physical or psychosocial sequelae. Patients and clinicians must then weigh the pros and cons of different options in order to make a decision. In this regard, procedures to assist in medical decision-making have been developed [78]. These have been evaluated in terms of patient satisfaction with the information given on aspects important to the decision, the decision made, and the consistency of the decision made with personal values [23]. Support for patient involvement in healthcare decision across the cancer care continuum need to be sustained as cancer patients appear to experience problems in that respect [79].

In addition, initiatives to improve the quality of care can be carried out in terms of the organization of care and services, including strategies for better coordination or continuity of care (e.g., care networks, supportive care department). Comparison of cancer care models can then take into account their effects on patient satisfaction. Various studies have been carried out: for example, the evaluation of a psychosocial intervention aimed at improving communication within a multidisciplinary team in charge of hospitalized oncology patients [80] or management methods within the framework of an oncogenetic approach [81, 82]. Other examples include the evaluation of different ways of organizing care for terminally ill patients [83] or the evaluation of the organization of a minimal or intensive medical surveillance programme after breast cancer treatment [34].

A recent model of care coordination in oncology based on "navigator patients"or "expert

patients" is increasingly being implemented to facilitate increasingly complex and fragmented cancer care. A navigator patient is an individual who assists the patient with information or practical support needs throughout the care process (i.e., screening, diagnosis, treatment, and surveillance phases). An "expert" patient is one who, with a chronic disease, has developed over time a detailed knowledge of his or her disease, has learned to live with it, and can thus be a resource for other patients. This approach should improve patient satisfaction in oncology; studies need to be developed on this subject [84].

Satisfaction with care is therefore a complex variable that depends, among other things, on patients' personal variables. However, it is an interesting measure that makes it possible to evaluate the impact of a medical follow-up with a patient and to improve the areas of dissatisfaction. Various tools have been developed in several areas of care such as technical, relational, and environmental aspects. Satisfaction requires further in-depth studies, particularly in relation to satisfaction with treatments. These results should be integrated in the transmission of information and more specifically within the framework of decision-making or informed consent.

15.5 Conclusion

Consideration of the patient's perspective regarding the quality of healthcare services is particularly important in oncology. Patients with cancer often face discomfort from the side effects of treatment and uncertainty about the nature, course, and prognosis of their condition. These situations are likely to lead to problems with treatment adherence, such as inappropriate attitudes towards treatment or refusal of treatment.

Research on satisfaction with care is working to better determine the influence of factors related to both patients and care. Although there are significant methodological difficulties and many questions remain, there is unanimity among researchers regarding the link between consideration of relational factors of care and high satisfaction. Indeed, it appears that communication skills fostering an in-depth exchange with the patient make it possible to ensure a better quality of care. Indeed, studies of satisfaction with care generally show high levels of satisfaction, particularly for aspects considered important for patients: technical skills and relational qualities of carers.

The development of morbidity associated with cancer conditions requires special measures and new strategies to maintain the comfort and promote patient recovery. Preparation and support programmes will therefore be necessary to face these difficulties. In recent years, we have seen doctors, nurses, and paramedics specialize in information science and/or psychoeducation. More research in this field is needed because optimal information and psychoeducation will have to take into account many different factors, clinical, psychological, scientific, ethical, and sociological. More than ever, the training of health professionals is indicated in order to offer quality interventions in this sector of care and their impact on satisfaction with cancer care.

15.6 Questions That Can Be Used for Learning/Testing

- Provide four arguments to justify the need to assess cancer patient satisfaction with care.
- List at least five objectives of satisfaction with cancer care assessment.
- List at least five dimensions of satisfaction with care.
- Which aspects of care most affect cancer patient satisfaction?

15.7 A Topic for Discussion That Can Be Used for Teaching

- Discuss how to interpret quantitative data collected from satisfaction with care questionnaires.

15.8 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

1. Neijenhuijs KI, Jansen F, Aaronson NK, Brédart A, Groenvold M, Holzner B, et al. A systematic review of the measurement properties of the European Organisation for Research and Treatment of Cancer In-patient Satisfaction with Care Questionnaire, the EORTC IN-PATSAT32. Support Care Cancer. 2018;26(8):2551-60 [39].
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3. Brédart A, Anota A, Young T, Tomaszewski KA, Arraras JI, Moura De Albuquerque Melo H, et al. Phase III study of the European Organisation for Research and Treatment of Cancer satisfaction with cancer care core questionnaire (EORTC PATSAT-C33) and specific complementary outpatient module (EORTC OUT-PATSAT7). Eur J Cancer Care (Engl). 2018;27(1) [32].
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15.9 Research in Context

The European Organisation for Research and Treatment of Cancer (EORTC) Quality of Life group conducts a research programme aimed at assessing satisfaction with care in oncology. A questionnaire, the EORTC PATSAT-C33, has been designed to assess cancer patients' perception of the quality of care received in any hospital care in- or outpatient setting. To complement this questionnaire, the EORTC OUT-PATSAT7 module has been developed to assess specific aspects of cancer outpatient perceived care quality. This module is to be used in complement to the EORTC PATSAT-C33 or as a standalone. These questionnaires have been developed through a rigorous process as recommended by the EORTC guidelines for quality of life questionnaires and modules development. An international study has been implemented to confirm the psychometric properties of scales of this questionnaire and module, in cancer patients attending in- and outpatient cancer care hospital services. The EORTC PATSAT-C33 and OUT-PATSAT7 will be investigated for cross-cultural applicability and acceptability, scale structure, reliability including test-retest and internal consistency, validity, including construct (known-group comparisons), convergent and divergent validity, responsiveness to change, and cross-cultural invariance of psychometric properties. These questionnaire and module are administered to four main groups of patients based on the cancer care settings which they attend, as outpatient: (a) chemotherapy day clinic/consultation for oral treatment; (b) ambulatory radiotherapy; (c) consultation for follow-up surveillance to check for signs of recur-

rence; and as inpatients: (d) an oncology or surgery ward. Patients are asked to complete these questionnaires at one moment during the treatment or remission phase of the disease trajectory. This assessment (T1) is performed (a) between 3 and 6 cycles of chemotherapy or after 2 cycles of other cancer treatment (e.g., biological therapy), (b) 2 and 6 weeks of radiotherapy, (c) after the 3rd to 24th month post-treatment, or (d) 3 days after hospital discharge.

The sample size is expected to be of 500 to ensure balanced patients' representation across outpatient cancer care settings and cross-culturally. For the test-retest assessment (T2), the aim is to include 125 patients for intraclass cluster correlation (ICC). Responsiveness to change is tested with a third assessment (T3) on a sub-sample of ~260 patients. Twenty institutions from at least four European regions and out of Europe are aiming to participate in the study during around a 25-month data collection period.

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16 Quality of Life and Cancer-Related Fatigue: Prevalence, Assessment and Interventions

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Contents

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16.1 Introduction

Fatigue is one of the most distressing symptoms for cancer patients affecting their quality of life (QoL) in all phases of treatment and stages of the disease. The syndrome of fatigue and exhaustion in cancer patients is commonly described as cancer-related fatigue (CrF). Other terms such as cancer fatigue or cancer treatment–related fatigue are also used in the literature and in educational materials for patients. CrF is commonly defined as a self-recognised phenomenon that is subjective in nature and experienced as a feeling of tiredness or lack of energy that varies in degree, frequency and duration which is not proportional to physical activities and not relieved by sleep or rest [1, 2]. Patients often describe CrF as an unusual feeling of exhaustion, weakness or a loss of activity with sequels to emotional and cognitive functions [1–3]. This chapter gives an overview about CrF as one of the most common side effects of cancer treatment. It will enable readers to understand the characteristics, the aetiology and the epidemiology of CrF. The reader will learn how to screen and assess CrF, and which treatment strategies are most appropriate.

16.2 Definition and Clinical Characteristics

As the most common definition, CrF is defined as a distressing, persistent subjective sense of physical, emotional and cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activities and interferes with usual functioning [4]. Typically, the symptoms do not decrease after recovery periods or sleep, and if at all, improvement only occurs for a short time [5]. CrF is not defined as a disease entity, but a concomitant syndrome of cancer [6].

In most publications, CrF has been described as a multidimensional construct including physical, cognitive and emotional dimensions [4]. The physical domain covers a loss of ability to perform activities due to somatic symptoms of tiredness and loss of energy. Depending on the type and intensity of the CrF, typical subjective perceptions include tiredness, heaviness of limbs, apathy towards external stimuli or even myalgias. Physical symptoms include muscular and metabolic changes, reduced muscle strength, tremor, diminished reflex responses, impaired coordination, electrolyte abnormalities, lactate increase and reduction of glycogen. The cognitive dimension includes loss of concentration, problems of attention, reduced alertness or impairment in short-term memory. The emotional dimension covers symptoms like loss of motivation, negative self-esteem, feeling of frustration and depressive feelings (Fig. 16.1).

Research has shown that fatigue may be a part of a complex regulation aimed to protect the body from harm [7]. The central nervous system may use the symptoms of fatigue and exhaustion as important regulators to ensure that an effort is stopped before it results in damage. Fatigue and increased fatigability are common reactions to physical and psychological distress but may also occur as symptoms in other medical and psychiatric conditions. Therefore, many chronic diseases such as rheumatoid arthritis, cardiovascular diseases or multiple sclerosis are associated with fatigue. Fatigue can occur as a concomitant symptom, or as in the case of depression, represent a main symptom. It is quite possible that fatigue has more than one simultaneous cause, even when it is associated with a clear diagnosis [8].

The clinical manifestation of fatigue in cancer patients (CrF) is multifaceted, and the perceived problems and limitations affect patients in a highly individual manner [9]. In comparison to healthy individuals who experience their fatigue as a normal sensation that is associated with daily activities, with CrF patients, the focus is on the feeling that already after a short time and at minimal exertion levels, physical exhaustion, fatigue, weakness and an unusually strong tiredness occur.

CrF often seriously impacts the QoL of patients and affects daily activities, work, sexuality or family life [10]. Ahlberg and colleagues found statistically significant negative correlations between fatigue and various domains of quality of life, including effects on physical,

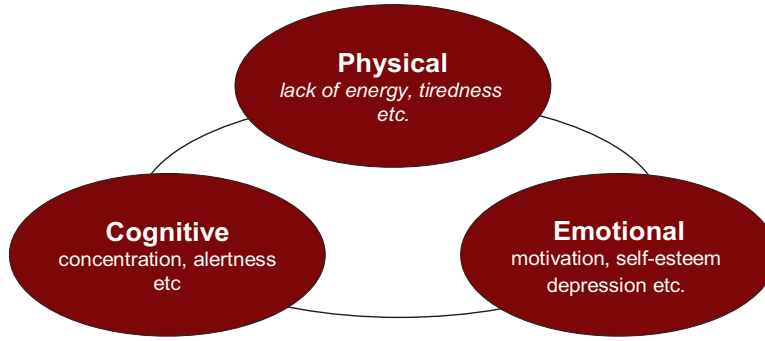

Fig. 16.1 Multidimensional structure of cancer-related fatigue [99]. (Reprinted by permission from Springer Nature: Definition and Prevalence of Cancer-Related Fatigue. In: *Cancer-Related Fatigue* by J. Weis and M. Horneber. Copyright © Springer Healthcare 2015)

emotional, cognitive, social functioning and role functioning [11]. They showed further that physical, role and cognitive functioning remained highly negatively correlated with general fatigue over time [11]. In addition, CrF does not only affect the individual patient but also the patient's partners or relatives [12]. Patients often report that persisting fatigue is not always understood by the people close to them and social conflicts arise which may result in social withdrawal or isolation. CrF has a significant effect on employment and financial status and has been proven to be a negative predictor for return to work after cancer [13, 14].

16.3 Aetiology and Pathogenesis

Until now, all attempts to explain the aetiology and pathogenesis of CrF failed to give a clear understanding about the pathogenesis of CrF. It is assumed that in CrF multicausal processes including somatic, emotional and cognitive factors are mutually dependent and interacting [15]. These factors are induced not only by cancer or cancer therapy but also by genetic predisposition, epigenetic changes, concomitant somatic or mental disorders, as well as through behavioural or environmental aspects [16].

Although the pathogenesis of CrF has not been completely clarified so far, some hypothetical explanations are discussed in the literature [17]. CrF often is associated with symptom clusters including mood disorders, sleep disturbances and cognitive dysfunctions which follow a similar time course in relation to treatment or disease [18, 19]. There is growing evidence that such symptom clusters may follow similar pathogenetic mechanisms.

Inflammation is discussed as the mediating process between the possible causes and the symptoms of CrF [20, 21]. Recently, proinflammatory mediators produced in response to cancer have been associated with fatigue; however, their direct role in pathogenesis of fatigue is controversial [16, 22].

In considering the relationship between immunological factors and CrF, a review of ten clinical trials has demonstrated that patients with CrF had elevated levels of markers for systemic inflammation [23]. In addition, it is known that chemotherapy and radiotherapy lead to an increase of numerous proinflammatory cytokines and chemokines [24–27]. The results of a longitudinal study suggest a link between CrF and increased soluble TNF receptor 1 and IL-6 levels during radiochemotherapy for colorectal and oesophageal cancer [28].

There is an overlapping in symptoms of CrF and clinical depression (e.g. tiredness, concentration, loss of motivation), whereas suicidal ideation, social withdrawal and anhedonia are more specific for major depression. Therefore, in some cases, it may be difficult to distinguish between both. In the literature, potential explanations are discussed: fatigue may cause the cancer patient to become depressed; cancer patients may become fatigued because they are depressed; or experience of cancer may cause both depression and fatigue [29, 30]. There is growing recognition that depression and CrF share common biologic mechanisms [16, 20, 31].

16.4 Epidemiology and Prevalence Rates

CrF is one of the most common symptoms in cancer patients and may occur either during or after medical treatment or as a long-term late effect after cessation of treatment. Based on several epidemiological studies, prevalence rates of CrF range from 59% to 100% depending on treatment modalities, cancer diagnoses or the time when CrF has been measured. In addition, the differences in the various prevalence rates may be explained by how fatigue is assessed, as well as which criteria for fatigue were used [32].

The degree, duration and frequency of CrF may vary over time [2]. Some studies have demonstrated that CrF usually increases during chemotherapy and decreases afterwards but may persist for up to 1 year or longer [33]. Comparing various treatment options, some studies have shown that severe CrF is more prevalent among patients receiving chemotherapy or concurrent chemoradiation compared with patients receiving only radiotherapy [34]. There is some evidence that treatment with opioids, poor performance states and weight loss are the strongest predictors for CrF [35]. In a retrospective study with mixed cancer diagnoses, women show higher level of CrF compared with men, whereas no difference was found comparing older and younger patients [36].

During the last two decades, a considerable number of studies have emphasised the complex problems faced by patients with cancer who experience CrF during treatment or afterwards. The highest prevalence rates were found for CrF as a direct side effect of a combination of medical therapies such as surgery, chemotherapy, radiotherapy, stem cell transplantation and hormone therapy [37, 38]. Higher prevalence rates for CrF are associated with the use of certain treatments such as hematopoietic stem cell transplantation (HSCT) or high-dose chemotherapy. Clinical studies investigating immune checkpoint antibodies, antiangiogenic agents and targeted therapies have reported higher rates of fatigue, ranging from 21% to 71% [39].

CrF has been documented for several specific cancer diagnoses. Lindendoll et al. showed in a systematic review on quality of life in lymphoma survivors that survivors of Hodgkin's lymphoma are at increased risk for fatigue when compared to healthy controls [40]. Heutte et al. found that high levels of fatigue at the end of treatment predicted persistent fatigue into long-term follow-up, but they did not find any differences between the treatment groups [41]. For patients with gynaecological cancer, prevalence rates between 20% and 58% are reported [42–44] and were identified as the most distressing symptom [45]. In a longitudinal study in patients with gynaecological cancer, CrF increased during treatment (chemotherapy, radiotherapy), whereas after completion of therapy, there was a slight improvement of the severity [46].

Previous findings reported that CrF as a long-term sequelae or late effect is estimated to have an average prevalence rate of approximately 30% for up to 10 years or more [35, 47]. In a large review and meta-analysis of 27 studies including 12,327 breast cancer survivors, it could be demonstrated that survivors with stage II or III cancer and survivors treated with chemotherapy were at higher risk for severe fatigue than survivors with lower stages [48]. Survivors treated with surgery, radiotherapy, and chemotherapy and survivors with this combination plus hormone therapy were at higher risk than survivors with other treatment combinations. Hormone therapy and targeted therapy were not significant risk factors. The pooled prevalence of severe fatigue was 26.9% (95% CI 23.2–31.0). According to this review, a relatively large decrease in the prevalence of severe fatigue seemed to occur in the first half-year after treatment completion. Overall, approximately one in four breast cancer survivors suffers from severe fatigue. Risk factors of severe fatigue were higher disease stages, chemotherapy and receiving the combination of surgery, radiotherapy and chemotherapy, both with and without hormone therapy. In addition, it was interesting that having a partner, receiving only surgery, and surgery plus radiotherapy decreased the risk [48].

In a prospective study, Fabi et al. investigated incidence, timing of onset, duration of CrF,

impact on QoL and psychological distress in patients with early breast cancer. The results show that prevalence of CrF was higher at the end of chemotherapy (CT) and lower at follow-up. At the end of CT and at 1 and 2 years after CT, persistence of CRF was associated with anxiety in 20%, 11% and 5% of patients and with depression in 15%, 10% and 5% of patients, respectively. A relationship between CrF and psychological distress was observed; patients presenting depression and anxiety before CT were at higher risk for fatigue onset at a later period [32].

For patients with Hodgkin (HL) or non-Hodgkin lymphoma (NHL), it has been documented that HL survivors showed increasing fatigue level with age, while in NHL survivors mean fatigue level remained constant until age 70 years and then increased with older age. HL survivors showed fatigue changes with age at a higher rate than those of the general population with health disorders, while NHL survivors were in between those of the general population with and without health disorders [49].

Prevalence of severe CrF is higher in patients with incurable cancer [50]. For patients receiving palliative or end-of-life care, CrF is associated with highly limited, or even loss of, body functions and overall quality of life [51].

16.5 Screening and Assessment

Assessment and clinical diagnosis of CrF is an important task of healthcare professionals in cancer care. According to the international guidelines [4, 52, 53], it is recommended to screen all cancer patients for symptoms of fatigue and exhaustion at regular intervals during treatment and after treatment has been completed. As a first step, a simple global numeric scale for assessing the intensity of the fatigue symptoms may be used. This global scale ranges from 0 = no fatigue to 10 = worst fatigue the patient could imagine [54]. For patients with age >12 years, a score of 0–3 has been identified as no fatigue to mild fatigue, 4–6 as moderate level of fatigue and 7–10 as severe level of fatigue (Fig. 16.2). The algorithm of screening and diagnostics of CrF in Fig. 16.2 is the recommended standard procedure for assessment and before planning of any therapeutic strategies.

As CrF is a complex and subjective phenomenon, it can only be measured by self-report assessment tools. Therefore, it has been commonly accepted that self-reports of patients are the most reliable and valid measurements of fatigue [55]. Comprehensive assessment of the fatigued patient includes a careful history to characterise the individual's fatigue pattern and to identify all factors that contribute to its development. To differentiate CrF diagnoses from other types of fatigue, specific diagnostic criteria were developed following the *International Statistical Classification of Diseases* (ICD-11) [3, 6]. The criteria define CrF as a syndrome including the 11 specific symptoms such as diminished energy or increased need to rest. The symptoms must have persisted during a defined period of time, caused significant distress or interfered with activities of daily living.

In addition, physical examination and behaviour descriptions by relatives are important sources for diagnosing CrF. Moreover, a review and adjustment of medications (e.g. cardiac medications, thyroid medications, sedative-hypnotic drugs, antidepressants) are needed, as the medication itself or interactions between different classes of drugs may contribute to increased fatigue [4].

Due to overlapping of symptoms of CrF with symptoms of depressive disorders [29], it is necessary to screen for psychiatric comorbidity, especially depressive disorders. The Patient Health Questionnaire 2-item (PHQ-2) may be used as a brief screening tool for major depression. The PHQ-2 consists of the first two questions of the Patient Health Questionnaire-9 (PHQ-9), which target core symptoms of depression (depressed mood and anhedonia) [56].

Due to the increased interest in fatigue among cancer patients, numerous instruments have been developed [57] using different methodologies. CrF may be assessed by either unidimensional or multidimensional instruments. Unidimensional instruments (e.g. FACIT Fa module [58] or the

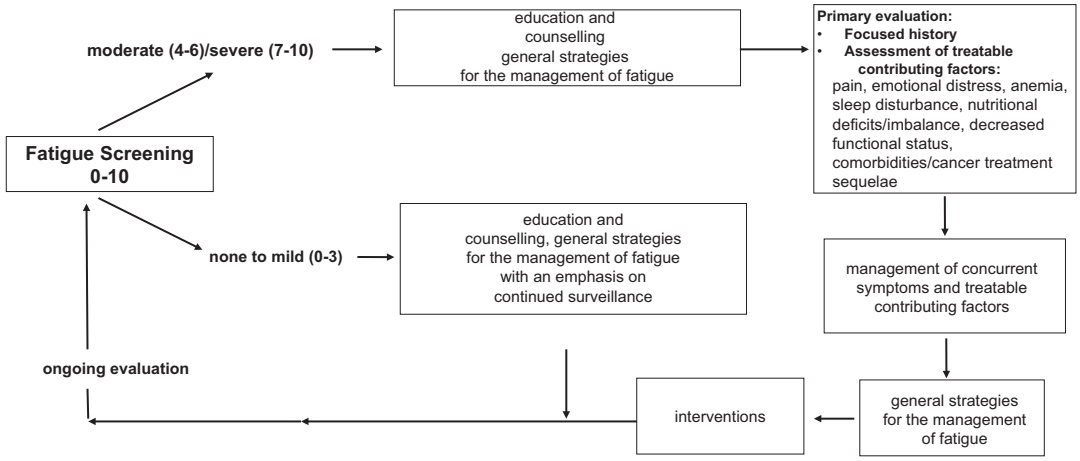

Fig. 16.2 Algorithm for assessment and treatment of cancer-related fatigue according to the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) (patients >12 years). (Adapted with permission from the NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) for Cancer-Related Fatigue V.1.2021 [4]. © 2020 National Comprehensive Cancer Network, Inc. All rights reserved. The NCCN Guidelines® and illustrations herein may not be reproduced in any form for any purpose without the express written permission of NCCN. To view the most recent and complete version of the NCCN Guidelines, go online to NCCN.org. The NCCN Guidelines are a work in progress that may be refined as often as new significant data becomes available)

Brief Fatigue Inventory [59]) are focusing only on physical symptoms of fatigue, whereas multidimensional instruments are addressing physical, affective and cognitive aspects of CrF. On behalf of the EORTC quality of life group, Weis et al. developed a cross-cultural validated module (EORTC QoL Fa12) [60] which has been proven for sensitivity over time [61] (see also Chap. 5, this volume). Most of the existing cancer-specific questionnaires are using a multidimensional approach to measuring CrF which is in line with an understanding of CrF as a multifaceted syndrome. In most questionnaires, the scaling pertains to intensity, but some are additionally asking for interferences with activities of daily living or quality of life. The existing questionnaires vary largely with respect to the criteria of validity, reliability, sensitivity to change or cross-cultural applicability. Methods used for supporting claims of construct validity include known groups comparisons, analyses for convergent and discriminant validity [52]. Moreover, cultural background is also influencing the way that fatigue issue is considered. In conclusion, while all of the reported fatigue measures have both strengths and limitations, there is no gold standard of which measure is more appropriate. The self-report approach with PRO questionnaires is the most common strategy in research and clinical routine. The decision on which instrument is used to assess CrF should depend primarily on the clinical setting or the research questions that are addressed.

16.6 Treatment Strategies

As mentioned earlier, in most cases there are no clearly diagnosed causes of CrF. Therefore, the treatment approaches are aimed at alleviating any factors that may be worsening the patient's CrF and to help the patient cope with the symptoms of CrF and the distress due to CrF. According to international guidelines, treatment should include strategies activating the patient's strengths and resources and should be initiated as early as possible, to prevent CrF from becoming a chronic problem [52]. The treatment approaches should address the individual needs in terms of physical, mental and cognitive symptoms; the extent of

functional impairment; and the patient's own understanding of the problem. Beyond specificities for subgroups, the following treatment options for CrF are available:

- Physical activity and exercise
- Psychosocial and psychoeducational interventions
- Pharmacological treatment

16.7 Physical Activity and Exercise

Physical activity, exercise and training have been proven as effective strategies to reduce CrF and help against the continuing decrease of physical functional status [62, 63]. Structured exercise programmes designed to improve a patient's skeletal muscle mass and strength and cardiovascular fitness, as well as aerobic endurance, can help the patients to reduce CrF and improve their overall quality of life [63]. Within the last two decades, many reviews and meta-analyses have demonstrated substantial evidence that moderate training in combination with relaxation techniques as well as body awareness reduce subjective fatigue levels and improve patients' quality of life. A Cochrane Review [62] shows moderate effects of physical training, especially for some subgroups of cancer patients and if applied early during ongoing adjuvant treatment. Although all existing guidelines and reviews recommend physical activity to cancer patients, frequency and intensity of exercise and training should be adapted individually depending on patients' age, clinical status of cancer and the level of physical fitness [64, 65].

Several meta-analyses demonstrated a significant reduction of CrF by exercise [66, 67]. In addition, in most reviews, symptomatic relief of depression, anxiety and pain also has been documented. Although there is a persuasive evidence for physical activity and exercise in reducing CrF over the whole trajectory of cancer, there is still a need for randomised clinical trials to investigate the effect of physical exercise in patients with advanced cancer.

16.8 Psychosocial Interventions

Psychosocial interventions for treating CrF include various types of interventions such as psychosocial counselling, psychoeducation, cognitive behavioural therapy and mind-body interventions [52, 68]. The main goals of the psychosocial interventions are to help patients understand the complexity of CrF, restructure their cognitive appraisal of CrF and change their coping strategies. In some of the psychosocial interventions, recommendations for physical activity or training are included.

Information and counselling may be a standalone intervention or a part of psychoeducational or other more comprehensive interventions. Information on the multifactorial nature of CrF and its potential causes and influencing factors help the patients to gain a better understanding of the complexity of CrF. Counselling can support the patients to devise a personalised activity plan, taking into account restrictions due to CrF [69]. Brochures or interactive media, including internet platforms, may be additionally used in the counselling process. Information and counselling also are provided for partners or relatives in order to prevent negative psychosocial implications.

Psychoeducational interventions are focused on empowering patients and enhancing their skills for self-management of CrF. The most important goal of psychoeducational intervention is to facilitate self-management [70, 71]. Against the background that emotional distress is highly correlated with fatigue, psychoeducational interventions help the patients develop problem-oriented coping strategies. Patients are educated to identify sources of psychosocial distress and to reduce stress-producing activities when possible [72, 73]. According to Fabi et al. (2020), psychoeducational programmes have been investigated in several studies demonstrating a significant reduction in CRF with small to moderate effects on CrF [52].

In the field of CrF, *cognitive behavioural therapy (CBT)* focuses on emotions, cognitive processes and maladaptive behaviour. CBT is used to improve adaptation to CrF by reframing dysfunctional thoughts and enhancing

goal-oriented activities (see also Chap. 19, this volume) [74]. CBT is generally used post-treatment and in the long-term, but it may also be used for patients with fatigue undergoing chemotherapy [75].

Corbett et al. identified in their review 33 studies investigating psychological interventions for CrF including a total of 4525 participants. Most interventions focused on psychoeducation, mindfulness, cognitive or behaviour therapy-oriented strategies. Twenty-three of the included studies reported a significant effect of the interventions on reducing fatigue in cancer survivors. However, studies differed widely in terms of measurement tools used to assess fatigue, mode, duration and frequency of the intervention delivery. In addition, RCTs were heterogeneous in nature and the number of high-quality studies was limited, definitive conclusions are not yet possible [76]. In a Cochrane review, only little evidence around the benefits of psychosocial interventions was found to reduce fatigue in adult patients with incurable cancer receiving cancer treatment with palliative intent. Especially for this subgroup, the authors concluded that additional studies with larger samples are required to assess whether psychosocial interventions are beneficial for addressing fatigue in patients with incurable cancer [77]. Recently, app-based psychoeducational interventions demonstrated effects in reducing CrF [78], but there is a need for further studies.

Mind-body interventions include a wide range of interventions classified as complementary medicine and supposed to work on a physical and mental level such as mindfulness-based stress reduction (MBSR) or yoga [79].

MBSR is a specific multimodal programme focused on improving well-being and health. It combines meditation exercises with cognitive-behavioural interventions and movement exercises. A meta-analysis showed effects of MBSR on global mental health of cancer patients [80]. Intervention studies documented improvements in various psychosocial outcomes, but most of the studies do not specifically use CrF as an outcome criterion. Therefore, more prospective randomised studies are needed [81, 82].

Yoga includes specific bodily postures, breath control and meditation, and has been investigated in several studies with cancer patients. Most of these studies addressed multiple outcome criteria including fatigue [83]. Yoga has been shown effective as a treatment to improve several symptoms and overall quality of life [84], but there is a need for more randomised controlled studies addressing CrF specifically.

16.9 Pharmacological Treatments

Among pharmacologic agents for the treatment of CrF, besides hematopoietics (only for anaemia) especially psycho-stimulants are discussed. There are some randomised controlled trials showing effects of methylphenidate [85, 86], especially for patients with severe levels of long-lasting fatigue and in progressive disease without psychiatric comorbidity. As possible side effects, vertigo, increased blood pressure and dryness of the mouth have been described [87]. Due to heterogeneous results [88], the use of methylphenidate is still discussed controversially. Effects seem to depend on the dosage used, the stage of cancer and the treatment setting. In some European countries, methylphenidate is not approved for use in CrF and taken as an off-label use.

Therefore, methylphenidate may not be regarded as a standard medication for treating CrF in the European guidelines [52], whereas National Comprehensive Cancer Network (NCCN) guidelines recommend psychostimulants for patients with moderate or high levels of fatigue during and after cancer treatment when other causes of fatigue have been excluded [4].

Modafinil was approved only for the treatment of narcolepsy, but it has been shown effective for treating CrF in only some studies [89, 90]. According to the European Society for Medical Oncology (ESMO) guidelines, modafinil cannot be recommended as a medication for CrF due to shortcomings in most of the studies [52].

Short-term use of *corticosteroids* is only recommended for PATIENTS with advanced or metastatic cancer, whereas long-term steroid use

should be avoided due to the possible side effects [91].

Moreover, there are some nutraceutical agents that are less well studied for their effects on CrF or have produced heterogeneous results. Among those that are currently the focus of clinical trials, the use of L-carnitine, coenzyme Q10, Wisconsin ginseng, astragalus, guarana and mistletoe are discussed controversially, and no clear recommendations for the control of CrF are given in the ESMO guidelines [52].

16.10 Conclusion

Among cancer-related symptoms, CrF shows the highest prevalence rates during and after oncological treatment and continues to be a substantial issue in long-term survivors. Although intensive research has been carried out within the last decades, a comprehensive model including somatic as well as psychosocial factors for understanding the multicausal development of CrF is still missing. For clinicians it is important to note that CrF is often not recognised and therefore must be routinely screened over the whole trajectory of cancer. For screening and assessment, some standardised unidimensional or multidimensional instruments are available to identify the individual level of CrF. Although many assessment tools have been developed, there is no gold standard for assessing CrF. An algorithm on how to assess and treat patients with CrF has been proposed to improve diagnostic and treatment planning in clinical care. Based on the diagnosis of the fatigue syndrome, international guidelines are available with recommendations for non-pharmacological and pharmacological interventions to reduce CrF. Comparing the various treatment approaches, physical exercise and psychological interventions are effective for reducing CrF during and after cancer treatment, and show significantly better results than the available pharmaceutical options [92]. Although considerable progress has been made in clarifying potential pathways of the pathogenetic mechanism of CrF and in developing treatment strategies, CrF is still to be regarded as a major challenge for research in the near future in order to better understand, prevent and treat CrF.

16.11 Questions That Can Be Used for Learning/Testing

- What are the typical symptoms of CrF?
- Which hypotheses are discussed as potential pathogenetic causes of CrF?
- Over the whole trajectory of cancer, in which phases may CrF occur?
- In which phase does CrF show the highest prevalence rate?
- Which symptoms show an overlapping of CrF with clinical depression?
- Which score in the screening scale is used as a threshold for a clinically relevant level of CrF?
- Which are the most effective interventions to reduce CrF?

16.12 A Topic for Discussion That Can Be Used in Teaching

Discuss the relevant factors that may influence CrF and propose a stepwise procedure on how to assess CrF and how to choose an intervention strategy to support the patient suffering from severe fatigue.

16.13 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

- Fabi A, Bhargava B, Fatigoni S, et al. on behalf of the ESMO Guidelines Committee. Cancer-related fatigue: ESMO Clinical Practice Guidelines for diagnosis and treatment. Ann Oncol. 2020;31(6):713–23. https://doi.org/10.1016/j.annonc.2020.02.016
- NCCN (National Comprehensive Cancer Network). Clinical practice guidelines in

oncology: cancer-related fatigue. V.1.2021. National Comprehensive Cancer Network, Inc.; 2020. Accessed 28 June 2021.
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16.14 Research in Context

The effective management of fatigue in patients with cancer requires a clear delineation of what constitutes nontrivial fatigue. The authors[a] defined numeric cut-points for fatigue severity based on functional interference and described the prevalence and characteristics of fatigue in patients with cancer and survivors. In a multicentre study, outpatients with breast, prostate, colorectal or lung cancer rated their fatigue severity and symptom interference with functioning on a numeric scale of 0 to 10. Ratings of symptom interference guided the selection of numeric rating cut-points among mild, moderate and severe fatigue levels.

The statistically optimal cut-points were ≥4 for moderate fatigue and ≥7 for severe fatigue. Moderate/severe fatigue was reported by 983 of 2177 patients (45%) undergoing active treatment and was more likely to occur in patients receiving treatment with strong opioids (odds ratio [OR], 3.00), those with a poor performance status (OR, 2.00), those who had >5% weight loss within 6 months (OR, 1.60), those who were receiving >10 medications (OR, 1.58), those with lung cancer (OR, 1.55) and those with a history of depression (OR, 1.42). Among survivors in complete remission or no evidence of disease, 29% of patients (150 of 515 patients) had moderate/severe fatigue that was associated with poor performance status (OR, 3.48) and a history of depression (OR, 2.21).

The current study statistically defined fatigue severity categories related to significantly increased symptom interference. The high prevalence of moderate/severe fatigue in both actively treated patients with cancer and survivors warrants the promotion of the routine assessment and management of patient-reported fatigue.
[a]Wang et al. [35].

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Quality of Life in Adolescents and Young Adults with Cancer

17

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17.1 Adolescent and Young Adult (AYA) Oncology: A Background

This chapter will provide an overview of the specific quality of life (QOL) concerns of adolescents and young adults (AYAs) living with and beyond a diagnosis of cancer. The QOL tools used with AYAs will be described and evaluated. Finally, AYA-specific interventions to help with the management of the impact of cancer will be explored.

By the end of this chapter, the reader will have an understanding of the following: (a) the unique qualities of AYAs in terms of cancer epidemiology as well as the complex interplay between their developmental and life stage and the challenges of a cancer diagnosis; (b) the QOL concerns of specific relevance and importance to AYAs; (c) tools used to assess QOL in AYAs; (d) the demand for QOL tools which are sensitive to the specific and unique concerns of AYAs and (e) interventions to help AYAs manage the effects of cancer on QOL.

17.1.1 AYAs as a Distinct Population

17.1.1.1 Definition of AYAs

Various age definitions have been used to describe the adolescent and young adult (AYA) oncology population, spanning from 13 years and extending up to 39 years [1]. In the UK, the importance of providing dedicated care provision and specialized treatment centres for AYAs aged between 16 and 24 years followed the 2005 National Institute for Health and Care Excellence (NICE) guidelines for improving outcomes in children and young people with cancer [2]. The definition proposed by the National Cancer Institute (NCI) with support from the LIVESTRONG Foundation in 2006 recognized AYAs as belonging to the 15–39 years age group at the time of first cancer diagnosis [3]. This wide age range was decided upon to best incorporate the entire AYA population and to give them a dedicated *home* in research and health care [3]. Regardless, the lower and upper age limits of the AYA definition are considered flexible and may be adjusted for research purposes [3].

17.1.1.2 Historical Background

AYAs form a distinct, understudied and underserved group within the oncology care setting that is often overlooked and stuck between paediatric and adult oncology, falling into a so-called "*no man's land*" [3]. As such, cancer in AYAs is an important health problem that has gone largely unrecognized and, due to a lack of research, relatively little is still known about their distinct biological and genetic characteristics [3]. Adding to this is the comparative lag in improvements of cancer survival (especially sarcomas) [4] and QOL outcomes that have been observed among AYAs in the past when compared with younger and older cancer patient populations [3, 5] and

resulted from more limited access to care, diagnostic delays, lack of dedicated treatment regimens and low clinical trial participation.

To raise awareness of AYAs as a distinct population in oncology and to improve cancer prevention, early detection, diagnosis, treatment, survivorship care and cancer-associated outcomes for this distinct population, various initiatives and charities have been organized over the years, including charities such as the Teenage Cancer Trust, Teen Cancer America and Canteen Australia. In 2006, the NCI partnered with the Lance Armstrong Foundation (LAF) to form The Adolescent and Young Adult Oncology Progress Review Group [3]. Based on this collaborative effort, a report on AYA oncology was released entitled *"Closing the gap"*, which provided a comprehensive list of national recommendations to improve AYA care and research initiatives, emphasizing enrolment of AYAs in clinical trials [3]. In the UK, a recent (2019) priority setting exercise involving AYAs, health professionals and caregivers was also carried out in collaboration with the James Lind Alliance (JLA) and identified psychosocial support for AYAs as a top priority [6, 7].

17.1.1.3 Unique Spectrum of Cancers

AYAs present with a unique spectrum of cancers that differs quite substantially from the distribution of cancers typically found among younger and older patients and includes an array of cancers frequently observed among children (e.g., acute lymphatic leukaemia), older adults (e.g., colorectal, lung and breast cancers) and a distinct subset of cancers unique to AYAs (e.g., Hodgkin's lymphoma, melanoma, germ-cell tumours and thyroid cancer) [5, 8–10]. A clear overview of these age-related differences in cancer type distribution is provided in Fig. 17.1 [10]. This figure further illustrates the sex-related variation in cancer type distribution within the AYA population. Although not presented here, the distribution of cancers also varies widely across the AYA age continuum, with carcinomas becoming increasingly more common from age 25 and beyond [5, 8, 9, 11]. As such, whenever possible, analysis of AYA data should distinguish between sex and age groups to avoid masking important trends.

17.1.2 Epidemiology of AYA Cancer

Despite the distinct oncology care focus on paediatric (aged 0–14 years) and older adult (aged ≥40 years) patients within the oncology domain, cancer at AYA age is diagnosed approximately six times more often at a global level when compared with the number of cancers diagnosed during the first 15 years of life [5, 9, 10]. For female AYAs, this ratio between AYAs and paediatric patients is even higher at around nine times (approximately four times in males) [10]. Although noticeable differences between continents exist, similar trends are observed worldwide, as shown in Table 17.1, which summarizes global estimates of all new cancer cases and relative frequencies (%) by continent, sex and age group in 2018 [10].

17.1.2.1 Incidence Trends

Although still considered rare, the incidence of AYA cancers has been on the rise for decades in most countries worldwide [8, 11–13] and includes cancers which are typically regarded as *older adult cancers,* such as those of the gastrointestinal tract, which have recently seen a decline in incidence amongst older patient populations [13–15]. In a recent examination of 41 countries over a 15-year period between 1998 and 2012, a clear rise in overall AYA cancers was observed in 23 countries [13]. Notable trends included a sharp increase in thyroid (in 22 and 33 countries, respectively, for males and females), testicular (22 countries) and obesity-related cancers (e.g., colorectal, uterus, pancreas, gallbladder and liver) [8]. In 2018, an estimated 1,231,007 AYA cancers were diagnosed, representing 6.8% of all cancer cases worldwide [10]. The majority of these cancers occurred in women (N = 799,079 [64.9%]), which can be explained by the large number of female-dominated cancers such as thyroid, breast, cervical and uterine cancers, all of which are common within the AYA cancer

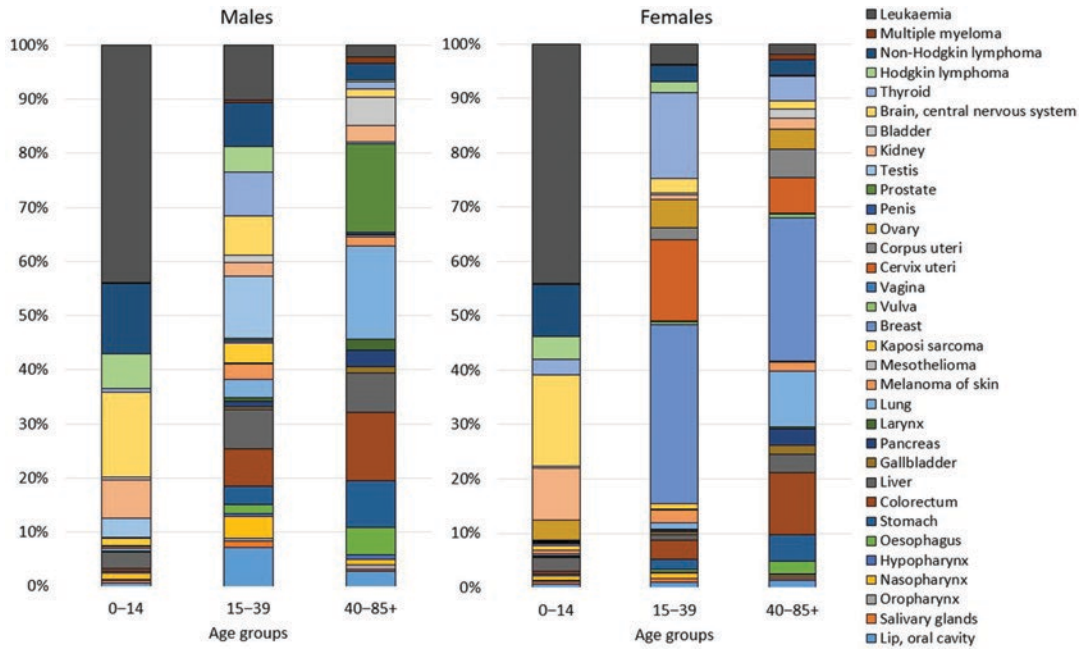

Fig. 17.1 Cancer type distribution presented by sex and age group based on global cancer data from the International Agency for Research on Cancer (IARC) for the year 2018. This figure illustrates the differences in cancer type distribution between both sexes and between children (0–14 years), adolescents and young adults (15–39 years) and older adults (≥40 years). (Data used is available from: https://gco.iarc.fr/today [10])

spectrum, especially among older AYAs aged 25 and beyond [8–12]. In male AYAs, the cancer spectrum in 2018 was dominated by leukaemia and testicular and thyroid cancers (Table 17.1) [10].

17.1.2.2 Survival and Mortality Trends

Among AYAs, cancer is responsible for approximately 25% of all deaths, making it the leading cause of disease-related death within this population in high-income countries [4, 5]. As stated previously, improvements in cancer survival among AYAs have historically lagged behind those observed in younger and older patient populations with similar disease [16, 17]. Nevertheless, the survival gap is beginning to close with survival among AYA cancer patients steadily improving over time with more effective treatment regimens and protocols and now often well exceeds 80% at 5 years of follow-up for all cancers combined [8, 11, 16–20]. Despite the relatively high overall survival, outcomes among AYAs have remained poor at <60% at 5 years of follow-up for certain cancers, such as lung, liver stomach, pancreatic cancers and most sarcomas [4, 8, 16, 17, 20]. Poor outcomes for these specific cancers is not exclusive to AYAs, but patients aged <50 years have been found to suffer from more aggressive disease with higher grade, more advanced stage and higher metastatic rates when compared with older populations [21–26]. Consequently, in some studies younger patients have shown survival outcomes that are similar or even worse compared to older patients whilst generally suffering from less comorbidities and despite being better capable of enduring treatment with more intensive regimens [22, 23, 26–28]. Furthermore, although encouraging, improved survival also translates into a growing population at higher risk of developing late effects, including secondary cancers, adding to the burden of morbidity (such as fatigue, pain, nausea, musculoskeletal problems and peripheral neurological symptoms) and premature mortality due to cancer in AYAs [5, 9, 29, 30]. Late medical

Table 17.1 Global estimates of new cancer cases in 2018 by continent, sex and age group

Continents	Males				Females			
	0–14	15–39	40–85+	AYA/paediatric ratio	0–14	15–39	40–85+	AYA/paediatric ratio
	N = (%)				*N* = (%)			
Asia	60,149 (1.3)	235,081 (5.0)	4,361,321 (93.7)	3.9	42,485 (1.0)	422,429 (10.3)	3,629,467 (88.6)	9.9
Europe	9388 (0.4)	55,314 (2.5)	2,182,816 (97.1)	5.9	8067 (0.4)	101,117 (5.1)	1,872,960 (94.5)	12.5
North America	6228 (0.5)	30,420 (2.4)	1,237,658 (97.1)	4.9	5722 (0.5)	55,869 (5.1)	1,042,888 (94.4)	9.8
Latin America and the Carribean	13,211 (1.9)	43,135 (6.3)	626,147 (91.7)	3.3	9919 (1.4)	83,445 (11.4)	636,875 (87.2)	8.4
Africa	24,825 (5.6)	61,894 (13.9)	359,837 (80.6)	2.5	18,824 (3.1)	128,370 (21.1)	461,422 (75.8)	6.8
Oceana	810 (0.5)	6084 (4.1)	142,100 (95.4)	7.5	538 (0.5)	7849 (7.6)	94,293 (91.8)	14.6
Total	114,611 (1.2)	431,928 (4.6)	8,909,879 (94.2)	3.8	85,555 (1.0)	799,079 (9.3)	7,737,905 (89.7)	9.3

This table highlights the percentage of new cancer cases for children (0–14 years), adolescents and young adults (AYA, 15–39 years) and older adults (≥40 years). The AYA/paediatric ratios show that cancer occurs several times more frequent among those at AYA age. (Data used is available from: https://gco.iarc.fr/today [10])

effects of treatment include pulmonary complications, cardiovascular complications, infertility, sexual and cognitive dysfunction, pre-term deaths, endocrine dysfunction, osteoporosis, kidney failure and neurotoxicity [31–34]. These problems are compounded in AYAs given the fact that they have among the highest number of life-years affected by cancer [4, 7, 16]. As such, the presence of long-lasting and late effects of the cancer and its treatment are likely to impact on QOL not just during treatment but beyond in the potentially lengthy survivorship years. Hence, increased focus should be directed towards primary and secondary prevention of AYA cancers as well as the development of treatment protocols with fewer side-effects without compromise to disease outcome. In addition, it is imperative to monitor and provide support and management of QOL concerns facing AYAs which, as will be discussed in the next section, are often unique in nature given the particular developmental and life stages AYAs are navigating themselves through.

17.2 Rationale for QOL Assessment in AYAs with Cancer

17.2.1 AYA Clinical Trials

One of the factors responsible for the poorer survival outcomes in AYAs compared with other age groups mentioned in the previous section is the lack of investment in and access to cancer research, and specifically enrolment in clinical trials which have historically been observed for this age group [19]. The reasons include a lack of recognition of this unique group of patients, regulatory factors, and lack of awareness and availability of trials. AYAs are also less likely to be enrolled in a clinical trial if they are older, uninsured and not treated by a paediatric oncologist [35–38]. To improve participation in trials, it is suggested to attend to the "5A's": appropriateness and acceptability of trial design, availability and accessibility of the trial, and awareness of the importance of trials [39].

One measure to improve access and availability of trials for AYAs would be to reduce the age limit of clinical trials for adult cancer patients, to include adolescents between 12 and 17 years [40, 41]. In terms of assessing QoL, it becomes important to have accuracy and consistency of measurement of QoL that cover the age range, to allow comparisons. Most QOL measures have been designed for and developed with adults aged 18 years and above. A way forward would be to validate widely used measures such as the EORTC QLQ-C30 [42] for this age group, while including QoL aspects that are particularly relevant to young people (see also Chap. 5, this volume).

17.2.2 QOL Assessment in Clinical Practice

QOL assessment can also play an important role within clinical practice with treatment toxicity and tolerability information harnessed from such assessments used to guide consultations by alerting clinicians to areas of concern which might require treatment modification or cessation or the implementation of management strategies to prevent treatment interruption, non-adherence and to improve well-being [43]. QOL measures allow for the capture of the impact of cancer and its treatment; going beyond symptoms to allow the AYA to communicate concerns and problems relating to psychosocial functioning, finances, education, work, fertility and sexual functioning which might not otherwise come up in the consultation, especially if the AYA perceives issues (such as impact on intimate relationships) as embarrassing or falling outside the realm of medical interest. QOL assessment can help clinicians understand how cancer fits into the life of the young person and his/her family and to tailor personalized support packages accordingly. In terms of long-term follow-up, QOL measurement can help identify and manage late effects.

The importance of establishing metrics to evaluate AYA care programmes has been recognized [44], and within the UK, the BRIGHTLIGHT prospective cohort study now

implements QOL assessments as part of the evaluation of teenage and cancer services [45].

17.3 QOL Issues in AYAs with Cancer

As with any age group, AYAs face numerous psychosocial and practical issues that impact on an individual's QOL when living with and beyond cancer and its treatment. Many of these issues, however, differ from older and younger patients due to the transitional period of life and the uncommonness of cancer in this age group. According to Erikson's psychosocial stages of development, individuals in this age range develop by defining a sense of physical self and personal identity, renegotiating relationships with parents or carers, establishing peer and romantic relationships and meeting the demands of increasingly mature roles and responsibilities [46]. Dealing with cancer and its treatment may interrupt these AYA-specific developmental activities leading to increased impact on QOL.

17.3.1 Biological QOL Issues

Not only is there a unique spectrum of cancers in AYAs compared to paediatric and adult patients, as described above, but the biology of the tumours and hosts may differ as well [47]. For example, AYAs tend to present with more aggressive forms of breast cancer than older patients [48] and more often with metastatic Ewing sarcoma compared to paediatric patients [49]. This may lead to AYAs receiving more intensive treatment and experiencing more side-effects or poorer clinical outcomes that can have an impact on QOL. One study of over 500 AYAs in the US showed that patients receiving both chemotherapy and radiotherapy had lower mental functioning than those receiving surgery alone [50]. Another recent longitudinal study showed that a poor prognosis (less than 50% chance of 5-year survival) in AYAs predicted significantly lower physical functioning [51].

17.3.2 Psychological QOL Issues

Evidence suggests that AYAs living with and beyond cancer have worse QOL in mental health domains than the general population and healthy peers [50, 52]. Fear of cancer progression or recurrence is more common in AYAs than in adults, with 85% of AYAs reporting fear of recurrence in one study compared to 80% of adults ($p < 0.001$) [53, 54]. This study hypothesizes that higher fear of recurrence may be associated with higher information needs and that interventions should aim to improve patient-provider communication. Fear of cancer recurrence has been identified as the cause for lower psychological functioning and decreased QOL, supporting the need for appropriate interventions [55].

Similarly, AYA age has been identified as an independent risk factor for distress and anxiety compared to other age groups with cancer again indicating the need for additional psychological support for AYAs [53, 56]. One longitudinal study following patients one year after diagnosis found that distress in AYAs reduced over time and was associated with being on treatment and uninvolved in school or work. Interventions should help facilitate AYAs' return to school or work if possible, to reduce distress [57].

Change in body image has also been identified as a particularly important issue for AYAs, especially for females [58]. In one study, 65% of females reported "looking like oneself" as very or extremely important compared to 42% of males ($p < 0.01$) [59]. In a narrative review of studies including children and adolescents, a number of studies found associations between lower body image and lower self-esteem, with low body image more common in females [60]. This review found inconclusive evidence regarding differences in body image in AYAs with cancer compared to healthy peers. The paper does, however, suggest that AYAs with cancer may have lower perceived body image after discharge or end of treatment as patients may be less concerned with image while on treatment.

17.3.3 Social QOL Issues

As the development of peer and romantic relationships is often an important aspect of AYA life, the interruption of social activities can have a particularly negative impact on QOL [61, 62]. AYAs often report feeling socially isolated as peers find it difficult to relate to the cancer experience and they have fewer opportunities for social interaction with time spent in hospital, unwell and avoiding infection [63, 64]. In a recent qualitative study, AYAs ages 14–25 identified activity limitations and social disruptions as important QOL issues [61].

Cancer and its consequences may also impact a young person's perceived ability to establish romantic relationships due to fears around disclosing the diagnosis, intimacy concerns, changes to body image and changes to fertility [65, 66]. Difficulty establishing romantic relationships can have a long-lasting impact. A recent systematic review showed that AYAs initiated their first romantic relationship later, had fewer romantic relationships and were less likely to marry than peers [67]. On the other hand, AYAs also report that cancer can have a positive impact in strengthening romantic relationships [66, 67].

Younger AYAs with cancer up to age 18 also report feeling a loss of independence needing to rely on parents for financial, physical, emotional and decision-making support [68] [69]. This loss can negatively impact an AYA's sense of control and QOL [69].

17.3.4 Practical QOL Issues

Practical issues are particularly relevant to AYAs with cancer. Most patients will be completing education or taking on new responsibilities such as establishing careers, having children or caring for older parents. AYAs over 26 years report a much higher burden of cancer on income and more financial toxicity than AYAs ages 15–25 years [70]. Practical issues with work and financial security are particularly high compared to older adults [53]. Primarily, financial strains are caused by loss of income in young adults [71]. Loss of income may contribute to high concerns related to living situation among young adults of working age compared to young AYAs and older patients [69].

Education and work attendance and performance may be compromised following a cancer diagnosis. AYAs who continue working or studying must navigate taking time away for clinic appointments and inpatient stays and manage side-effects such as fatigue and pain while trying to complete work and assignments [61]. Older AYAs report that childcare responsibilities also pose barriers to attending follow-up cancer care appointments [72]. In addition, treatments often leave patients immunosuppressed, requiring AYAs to avoid "high-risk" settings such as the workplace and schools/colleges [61].

Furthermore, cognitive impairment can last decades after treatment and impact education and vocational attainment and result in altered career plans [73, 74]. This can have a particularly large impact on AYAs given the long period of survivorship. Poor educational attainment amongst AYAs with cancer is associated with increased likelihood of post-traumatic stress and emotional distress [75]. Certain tumour types that require more intensive treatment may be at higher risk of reduced attainment. For example, AYAs diagnosed with haematological malignancies are less likely to be in work or education in follow-up which may lead to lower quality of life [51].

17.3.5 Fertility

Reproductive concerns are unique to AYAs as the group encompasses the child-bearing years [69]. AYAs and their families may feel conflicted when deciding between starting treatment urgently and preserving fertility, especially in the case of young women where fertility preservation techniques are invasive and introduce time constraints [65]. Many AYAs also feel under-informed about the risks of cancer and its treatment on fertility [76, 77]. Women who receive less specialist counselling about fertility are more likely to experience decisional regret and lower QOL [78]. Compared to healthy peers, AYAs also have

lower satisfaction in sexual function with females reporting lower frequency of orgasm and males reporting lower sexual desire which may contribute to fertility issues [79].

17.3.6 Positive QOL Issues

As outlined in the previous section, a diagnosis of cancer is traumatic for any age group but for those during adolescence and early adulthood, it can be hugely disruptive due to the developmental tasks which need to be negotiated during this phase of life. Not surprisingly, the physical and psychosocial impact of cancer and its treatment on AYAs is typically viewed through a negative lens and this is reflected in the QOL measures presented in the next section of this chapter with lower incidence of problems and higher functioning equating to a better QOL. However, there are reports of AYAs finding positives through their cancer experience and descriptions of cancer as a catalyst for positive changes in life [61, 80–82]. Positive changes have even reported by AYAs early in the cancer trajectory, i.e., during treatment [61], and thus, the perception of positivity is not just reserved for a time when the AYA is cancer free and can reflect back on the experience without the burden of treatment and the anxiety surrounding outcomes.

As part of the Adolescent and Young Adult Health Outcomes and Patient Experience (AYA HOPE) Study [83] investigating the psychosocial impact of cancer on 523 AYA survivors, several positive life impacts were identified alongside negative effects of cancer. The percentage of AYAs recognizing a positive impact surpassed the percentage of negative and neutral responses on domains such as relationships with partners/spouses, parents and siblings (>75% of respondents), plans for the future and goal setting (around 46%), health competence, defined as confidence in one's ability to take care of health (around 40%), and spiritual and religious beliefs (>50%). Positive changes in how AYAs view themselves in terms of a greater sense of maturity, life including a re-evaluation of priorities and greater motivation to achieve personal and academic goals and relationships with others including opportunities to forge new friendships and a realization of true friends have also been reported [61]. Benefit finding in illness such as cancer can be interpreted as a form of coping such as "positive reappraisal" or "positive refocusing" which has been found to be associated with less distress and better adaptation to illness and confidence to manage future challenges [84, 85]. The potential of reframing thoughts relating to cancer is the impetus behind interventions to improve psychological well-being, QOL, self-esteem and self-efficacy [86]. Interventions for AYAs with cancer will be explored in more detail later in this chapter.

Given the accounts of positivity in the AYA oncology literature and that benefit finding in cancer has been identified as associated with younger age [87], it is important to explore positive changes when monitoring the impact of cancer and its treatment on AYAs, associated with younger age. That is not however to say that acknowledging the positive impact of cancer undermines or rules out the negative and wide-ranging effects presented in Sect. 17.3, rather it allows us to better understand the experience of AYAs and the role such positive appraisals might play in their adjustment to cancer.

17.4 QOL Measurement in AYAs with Cancer

As highlighted earlier in the chapter, monitoring QOL concerns and challenges experienced by AYAs is imperative for the delivery of optimal care of AYAs with cancer from diagnosis, through treatment and beyond. QOL assessment can lead to prompt and effective management of issues and facilitate patient-clinician communication and decision making [88].

The need for developmentally relevant, psychometrically sound measures embracing the entire age spectrum of AYAs with cancer and appropriate for varying levels of literacy and cultural backgrounds has been emphasized [3, 12]. Generic tools (non-disease specific or non-tumour type-specific [42, 89, 90]), which were developed

with and designed for older adults, have been used with AYAs but lack sensitivity to the unique concerns of this age group. Identifying reliable and valid AYA appropriate measures of QOL covering all the relevant multi-dimensional aspects of QOL of importance to AYAs across the entire age spectrum is challenging [91, 92] not least because of the lack of congruence in defining AYAs, as well as the differing conceptualizations of QOL itself. *Cancer-specific* measures which have been developed specifically or adapted from adult or paediatric measures for AYAs with cancer either during treatment or post-treatment are presented in Table 17.1. (Note, we have not included in this table measures which were developed for AYA survivors of childhood cancer.) Of the 16 measures identified, seven [93–99] were developed with and specifically for AYAs with cancer. Only one measure, the Late Adolescence and Young Adulthood Survivorship-Related Quality of Life (LAYA-SRQL) measure [98], covers the wide AYA age spectrum (15–39 years), to include adolescents, emerging adults and young adults; however, this measure is appropriate for AYA survivors rather than AYAs with active disease currently receiving treatment. An additional six measures are identified as appropriate for completion by young adults beyond the age of 18 years, which is the common cross-over point for adult measures. Several of the measures identified [93, 94, 97, 100] have their roots firmly embedded within the childhood years. Most of the measures in Table 17.2 which have been adapted for AYAs were originally paediatric measures with only the young person versions of the Functional Assessment of Cancer Therapy Questionnaires in brain tumour survivors (pedsFACT-BrS) [101] and for cachexia (peds-FAACT) [102] representing adaptations of adult measures. In addition, the adapted measures tend to cover the adolescent years only.

The measures differ in terms of QOL focus and the domains measured with the majority representing multi-dimensional tools capturing the broad range of QOL concerns. Some of the measures are narrower in focus measuring one aspect of QOL, such as unmet needs, symptoms and reproductive concerns and can thus be defined as purpose specific. Some of the measures are further refined in focus in terms of including only questions of relevance to a specific tumour group such as testicular cancer [95] or bone tumours [97]. The length of measures varies between 10 questions for the uni-dimensional measures of peds-FAACT [102] and the adolescent version of the Reproductive Concerns Questionnaire [103] and up to 90 questions for the Cancer Assessment for Young Adults – Testicular (CAYA-T) [95]. Most of the multi-dimensional measures of QOL include questions relating to the physical, psychological and social impact of cancer. Some measure broader aspects such as [95] education and work [95, 96], sexuality [95, 98] and reproductive [90] concerns. However, issues of importance to AYAs such as fertility, financial and body image concerns as well as positive issues are largely absent from the measures identified.

The measures also vary in terms of their development process, not just in terms of their starting point, i.e., whether they were originally designed for AYAs or adapted from paediatric or adult measures, but also in terms of the level of young person input in the measure's development stages and the psychometric testing in terms of reliability and validity. The Adolescent Quality of Life Instrument (AQoL) [93], for example, has been criticized for the lack of young person, parent or expert involvement in its development and the paucity of information supporting its psychometric properties [104]. In contrast, as part of the development of other measures such as the pedsFACT-BrS [101], the Quality of Life of Childhood Cancer Adolescence Form (QOLCC-ADO) [105] and the PedsQL™ [106], young people were interviewed or involved in focus groups with their experiences informing the content of the measures, along with expert opinions and reviews of the literature, and thus, such measures are likely to have enhanced content validity in terms of measuring what matters to AYAs.

Electronic capture of symptom and QOL data from AYAs is a feasible and promising option to allow for the collection of complete and accurate information from AYAs in real time [107] and to prompt early intervention and management where necessary.

Table 17.2 AYA cancer-specific measures measuring QOL

(a) Measures for AYAs on and off treatment				
Measure and authors	Intended age group	Focus	Number of questions	Domains/sub-scales
AYA specific measures				
Adolescent quality of life instrument (AQoL) Ward-Smith et al. [93]	Pilot tested with young people aged 9–20 years	Self-evaluation of QOL by adolescents with cancer	16	Normal activities Social/family interactions Health status Mood Meaning of being ill
Behavioural affective and somatic experiences scale (BASES) Phipps et al. [94]	Developed with children and young people up to 20 years	Acute and short-term psychosocial outcomes in children undergoing bone marrow transplant (BMT). Applied to other settings to assess the effects of active intensive treatment	14	Somatic distress Compliance Mood/behaviour Interactions Activity
Cancer assessment for Young adults – Testicular (CAYA-T) [95] Hoyt et al. (2013)	18–29 years	QOL of young men with testicular cancer	90	Physical Sexual Intrapersonal Social-relational Educational/ vocational/ avocational Spiritual
Cancer needs questionnaire-Young people (CNQ-YP) Clinton-McHarg et al. [96]	14–25 years	Unmet needs of AYA patients with cancer and survivors *Purpose-specific (unmet needs)*	70	Treatment environment and care Feelings and relationships Daily life Information and activities Education Work
AYA versions of measures				
Pediatric functional assessment of anorexia and cachexia therapy (peds-FAACT) Lai et al. [102]	7–17 years (adolescents defined as 12–17 years)	Concerns specifically associated with anorexia and cachexia in children (adolescents) with cancer	10 (6 core items for children 7–17 years; 4 additional peripheral items for patients 10–17 years)	Anorexia and cachexia
KINDL cancer Kiddo Ergin et al. [111]	13–16 years	Measure QOL in young people (adolescents with cancer)	24	Physical Mental Social relations Treatment
Memorial symptom assessment scale (MSAS 10–18) Collins et al. [100]	10–18 years	Provide multidimensional information about a diverse group of common symptoms in the (older childhood) cancer population	30	Physical Psychological Global symptom distress

(continued)

Table 17.2 (continued)

(a) Measures for AYAs on and off treatment

Measure and authors	Intended age group	Focus	Number of questions	Domains/sub-scales
Pediatric advanced care quality of life scale (PAC-QoL) Cataudella et al. [112] *Teen self-report*	13–18 years	Measure QoL in children with poor prognosis malignancies e Q Measure QOL in children (adolescents) with poor prognosis malignancies	59	Physical comfort Psychological Well-being Social interaction Resilience Quality of care
Pediatric Quality of Life Inventory (PedsQL)™ Cancer Module Varni et al. [106] *Adolescent form* *Young adult form*	13–18 years 18–25 years	Measure QOL in children (adolescents; young adult) with cancer (self-report and parent versions)	27	Pain and hurt Nausea Procedural anxiety Treatment anxiety Worry Cognitive problems Perceived physical appearance Communication
Pediatric cancer quality of life Inventory-32 (PCQL-32) Varni [113] *Adolescent form*	(child 8–12 years) 13–18 years	QOL in children (adolescents) with cancer	32	Disease- and treatment-related symptoms/ problems Physical functioning Psychological functioning Social functioning Cognitive functioning
Quality of life of childhood cancer adolescence form (QOLCC-ADO) Yeh and Hung [105]	13–18 years	Impact of disease and treatment on child's (adolescent's) appraisal and satisfaction of function	34	Physical functioning Psychological functioning Social functioning Treatment/ disease-related symptoms Cognitive functioning

(b) Measures for AYAs post-treatment only

Measure and authors	Intended age group	Objective	Number of questions	Domains/ sub-scales
Bt-DUX Bekkering et al. [97]	Developed with young people aged 8–25 years	Evaluate QOL in young people who have had surgery for lower extremity malignant bone tumour *Tumour specific* Lower extremity bone tumour	20	Social Emotional Cosmetics Physical

(continued)

Table 17.2 (continued)

(b) Measures for AYAs post-treatment only				
Measure and authors	Intended age group	Objective	Number of questions	Domains/ sub-scales
Late adolescence and young adulthood survivorship-related quality of life measure LAYA-SRQL Park et al. [98]	15–39 years	To assess the experience (satisfaction and impact) of LAYA cancer survivors	30	Existential/ spirituality, coping Relationship Dependence Vitality Health care Education/ career Fertility Intimacy/ sexuality Cognition/ memory
Quality of life in children and adolescents with cancer PEDQOL Calaminus et al. [99]	Pilot tested with young people aged 8–18 years	QOL evaluation in survivors of cancer during childhood and adolescence	34	Physical functioning Autonomy Emotional functioning Cognition Social functioning/ friends Social functioning/ family Body image
Reproductive Concerns Instrument Wenzel et al. [103] *Adapted for adolescents* Quinn et al. [114]	Developed with young adults aged 17–24 years and adapted for adolescents aged 12–18 years	Concerns among survivors whose reproductive ability may have been impaired or removed due to disease and/or treatment	Original scale: 14; adapted adolescent version: 10	Total reproductive concerns scale
AYA versions of measures				
Pediatric Functional Assessment of Cancer Therapy Questionnaire (Version 2.0) in brain tumour survivors pedsFACT-BrS Lai et al. [101] *Adapted for adolescents* Yoo et al. [115]	Developed with children aged 7–11 years. Adapted for adolescents 13–18 years	Post-treatment (at least 1 year since treatment) QOL in children (adolescents) with brain tumours	37 (25 generic cancer concerns and 12 brain tumour survivor-specific concerns)	Physical Well-being Emotional wellbeing and illness experiences Social or family Well-being Brain tumour survivor-specific

The impact of cancer on the QOL of AYAs is often interpreted within the framework of developmental psychological theories which include a focus on achieving conventional milestones including educational attainment, career achievement, marriage and children [108]. Recently, researchers have advocated considering the changing social and global context including norms and expectations in theoretical frameworks for AYA research to better take the heterogeneity of AYAs into account [109, 110]. These changes include differing life goals and timetables, such as interest in having children later or not having children at all, sexual and gender plurality, expanding cultural diversity and rapidly developing technological environments [109, 110]. It is important for QOL measurements to be responsive to societal and cultural changes and this might require an updated and more flexible approach to QOL assessment for this age group.

The selection of a suitable measurement tool for AYAs is driven by several factors. Firstly, the intended age group for measurement needs to be considered and whether the measure includes questions appropriate for respondents across the entire AYA age range or whether the focus is just on adolescents, emerging adults or those in early adulthood. Secondly, the extent to which the questionnaire has been validated and has demonstrated reliability with the intended age group. Finally, the choice of measurement tool is governed by the purpose or focus of the investigation, i.e., whether the domains covered in the instrument suit the area of interest or concern.

17.5 AYA-Specific QOL Interventions

Various interventions have been developed to address QOL issues experienced by AYAs. These range from one-to-one professional support to digital support. Many of these have been evaluated for usability and feasibility; however, few have been rigorously tested for effectiveness. Here we focus on interventions that have demonstrated improvements in some aspect of QOL.

17.5.1 Communication

Patient-provider communication is important for eliciting relevant QOL issues. According to the Adolescent Resilience Model, provider support may be a key protective factor in AYA well-being [116]. One intervention developed by researchers to improve patient-clinician communication led to reduced variability in the number of topics discussed with AYAs [117]. This paper-based "Snapshot" intervention showing a map of potential concerns prompts conversation around psychosocial issues between patients and social workers. Another intervention comprised a mobile phone app for symptom tracking improved patient-clinician communication by visually displaying symptom severity and frequency in an objective manner [118]. Patients involved in this trial also indicated the tool facilitated conversations about personal or sensitive topics.

17.5.2 Psychosocial Interventions

Multiple studies have shown unmet need for psychological support in AYAs [119, 120]. One-to-one psychological counselling has shown to improve QOL. One study offering three counselling sessions on challenges related to cancer, social or family relationships and couple or sexual relationships improved overall QOL and illness-related self-efficacy [121]. Another one-to-one intervention based on cognitive behavioural therapy improved resilience and cancer-specific QOL and reduced psychological distress [122]. This intervention included four sessions focusing on stress management, goal setting, cognitive restructuring and benefit finding (see also Chap. 20, this volume).

Less conventional therapies have also shown to have a positive effect on AYA psychosocial outcomes. A therapeutic intervention allowing AYAs to direct a music video while engaging with their family, friends and environment and reflect on their experiences improved courageous coping and social integration [123]. Another video game intervention resulted in improved self-efficacy although it did not impact on QOL [124].

17.5.3 Electronic Monitoring of Symptoms and Side-Effects

A number of digital interventions have been developed specifically for AYAs to help empower them and develop their confidence (self-efficacy) to manage symptoms and side-effects as well as promptly alerting clinicians to potential problems and the need for treatment modifications or implementation of management strategies. Evaluations of such interventions suggest that they are acceptable and usable [125] and have demonstrated improved perceived self-efficacy as well as emotional and social functioning and overall QoL [118, 126] (see also Chap. 8, this volume).

17.5.4 Physical Activity Programmes

While exercise has long been acknowledged as playing a fundamental role in primary and secondary cancer prevention, it has more recently gained momentum as a potential adjunct therapy following a cancer diagnosis in terms of mitigating and managing the effects of cancer and its therapy such as fatigue and improving physical function and QOL [127]. The benefit of physical activity interventions following a cancer diagnosis has been demonstrated in the AYA population [128]. Physical activity programmes have also used digital and social networking platforms to facilitate their delivery [129, 130] and provide strategies to increase physical activity including enlisting social support, incorporating exercise into daily activities, problem-solving and self-monitoring. While there is evidence for the therapeutic tolerability and acceptability of these interventions, evaluations of their efficacy are limited especially with respect to improvements to QOL [129, 130].

17.5.5 Fertility Counselling

Fertility preservation is an important and complex issue unique to AYAs with cancer. Fertility preservation can be a particularly complicated issue for females as treatment options require invasive procedures and may delay the start of anti-cancer treatment [131]. Unmet information needs and fertility concerns are associated with decisional conflict [132]. Consultation with a fertility specialist about potential reproductive loss and undertaking fertility preservation options is associated with reduced decisional regret and improved QOL in women of childbearing age with cancer [78]. From a service delivery perspective, providers found that the combination of interventions that established referral pathways, implemented quality indicators, educated health professionals and provided patient information nearly doubled the likelihood of specialist referral in women [133]. In an evaluation of the introduction of interventions to improve clinical practice associated with fertility preservation in young people with cancer, women and men were nearly two and three times as likely to undergo fertility preservation, respectively, compared to prior to the implementation of the interventions [133]. From the patient perspective, evidence suggests that web-based decision aids complementing fertility specialist consultations contributes to improving fertility knowledge and reduces decisional conflict for young women with cancer [134, 135].

17.6 Conclusion

In this chapter, we have presented AYAs with cancer, commonly defined as those diagnosed between the ages of 15 and 39 years, as facing unique concerns which impact on their QOL; they find themselves at a point in life where they are already having to negotiate other challenges and, in terms of their treatment and care, they often straddle paediatric and adult care services. It is also acknowledged that AYAs still lag behind their younger and older counterparts in terms of survival outcomes. It is only within the last 10–15 years that AYAs with cancer have become increasingly recognized as a patient group in their own right with more AYA dedicated oncology centres opening in hospitals and a drive towards increased clinical trial participation. This changing landscape of AYA oncology is largely attributable to national agendas focusing on improved AYA services, more research dedicated to

reporting outcomes and interventions for this age group as well as the significant contribution of AYA cancer charities. Monitoring QOL of AYAs from the point of their cancer diagnosis, throughout treatment and beyond helps us to understand the experience of AYAs, both positive and negative as well as triggering personalized support where needed. QOL assessment also plays a key role in the evaluation of new treatments as well as AYA services. If QOL assessments are to be implemented as part of routine clinical care for AYAs with cancer and respected as a valuable outcome in research studies and trials, it is imperative that we have a tool that is in tune with the broad and specific concerns of this age group and thus measures what actually matters to AYAs; there is currently no gold standard measure of QOL for AYAs.

17.7 Questions That Can Be Used for Learning/Testing

To what extent can we extrapolate from the experiences of other age groups (older adults and children) when understanding the QOL concerns of AYAs with cancer?

Why should we measure QOL in AYAs with cancer?

In what ways can interventions help AYAs manage cancer and its treatment?

17.8 A Topic for Discussion That Can Be Used for Teaching

What factors influence decisions relating to selecting a measure to assess QOL in AYAs with cancer?

17.9 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

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17.10 Research in Context

A Collaborative Approach to QOL Assessment of AYAs with Cancer

As mentioned in Sect. 17.5 of this chapter, there is no shortage of QOL measures which have been used with AYAs with cancer, but there is no gold standard measure which encompasses all aspects of QOL specific to a group of patients who are heterogeneous not only clinically but also developmentally and what stage of life they are at; issues relevant for teenagers are likely to be hugely disparate from those facing adults in their thirties. Thus, there is currently no perfect recommendation for the optimal measure for assessing QOL in AYAs with cancer. Current QOL measurement strategies used with AYAs with cancer were critiqued in a recent commentary [92]. The authors emphasized the need for a psychometrically robust methodology in order to capture all relevant QOL issues for AYAs which are often overlooked in existing measures. The application of the National Institutes of Health's Patient-Reported Outcomes Measurement Information System (PROMIS) was advocated as an optimal strategy with the option of either using existing PROMIS measures or adopting the PROMIS methodologies to develop new measures to address gaps in QOL content. In a reply to this commentary [136], the EORTC Quality of Life Measurement system with its item library was presented as an alternative strategy [137], comparable to the PROMIS in terms of its flexibility of use as well as offering the potential to create bespoke measures with the application of Computer Adaptive Testing techniques [138]. While the papers present different recommendations in terms of measurement strategy (PROMIS vs. EORTC), there is agreement regarding the need to harmonize efforts to form an international collaborative thus profiting from the rigorous and robust work which has already been performed.

The development of core outcome sets (COS) for AYAs with cancer would support such a collaborative endeavour. COS may be developed for research or clinical practice and are determined by consensus amongst health professionals, researchers, policymakers and patients or their representatives, thus ensuring the priorities and expertise of these key stakeholders determine the most important outcomes to measure for a given condition. COS are increasingly being recommended for use by trial funders and healthcare organizations [139] and would pave the way for a more coherent approach to measuring what really matters to AYAs so that we can better understand their experiences and improve health outcomes.

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Proxy Measures for Quality of Life in Cancer

18

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Contents

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18.1 Introduction

Missing data are a challenge in cancer research, including research for quality of life (QOL) and other patient-reported outcomes (PROs). In cancer, missing data may arise for many reasons. Patients may not wish to complete items on PRO assessments, or PRO assessments themselves. Patient ill-health, either due to the disease itself or the side effects of treatment, may prevent patients from completing assessments. These concerns are particularly salient when assessing QOL at the end of life. Cognitive problems arising from brain tumours or metastases may raise concerns about patients' ability or willingness to complete self-reported measures. In paediatric oncology, some patients may be too young to complete PRO assessments. One approach that has been used, particularly in health surveys, has been to use proxies to answer on behalf of patients. The proxy answers instead of the patient, thus avoiding what would be otherwise missing data.

However, there are concerns about the use of proxy reports. Proxy and patient reports are not equivalent and proxy-patient discrepancies regarding patient QOL, symptoms and function are well known. The use of proxy reports can affect QOL estimates. Proxy reports have been discouraged by regulators: the European Medicines Agency (EMA) suggests that proxies only be used as a last resort [1], and the US Food and Drug Administration (FDA) prefers observer-reported outcomes to proxy-reported outcomes [2]. However, in non-regulatory settings, including surveys, epidemiologic studies and end-of-life or bereavement assessments, there are often few, if any, alternatives to using proxies.

This chapter will discuss the use of proxies in cancer. We will discuss the use of proxies and proxy measures in research, including the types of proxy measures available and the considerations needed for proxy and proxy measure use. This chapter enables readers to: (a) become familiar with proxies and proxy measure; (b) determine the advantages and disadvantages of using proxies; (c) assess how proxy measures have been used in research and care; and (d) understand the key considerations and issues when using proxies in research and care.

18.2 Proxies and Proxy Measures

18.2.1 What Is a Proxy and What Is a Proxy Report?

A proxy is an individual who provides information about a patient who cannot or will not self-report. The use of inconsistent terminology regarding proxies can be a source of confusion. In the 2009 guidance regarding the use of PROs in drug and device labels, the FDA defined a proxy-reported outcome as "A measurement based on a report by someone other than the patient reporting as if he or she is the patient" [2] (p. 32). This is differentiated from an observer-reported outcome, where an observer "report[s] his or her observation [and] may interpret or give an opinion based on the observation" [2] (p. 32). The guidance also notes that observers can be "clinician[s] or caregiver[s]" [2] (p. 32). The EMA, like the FDA, highlights the proxy taking on the patient's perspective when reporting, but views observer-reported outcomes as being pro-

vided by a caregiver who is not a clinician [1]. One challenge with this definition is that proxies may be asked to report from other or multiple perspectives, and the perspective used is not always reported [3]; thus, differentiating between proxy and observer reports, and thus proxies and observers, may not be clear-cut.

The FDA later sought to further differentiate proxy-reported and observer-reported outcome measures. Specifically, observer-reported outcome measures were "limited to the assessment of observable signs and symptoms that can be reported from the perspective of a parent or caregiver" [4] (p. 17), whereas in proxy-reported outcome measures "someone other than the patient reports on patient symptom experiences as if he or she is the patient" [4](p. 17). Likewise, the EMA views observer-reported outcome measures as being limited to strictly observable events or behaviours, which suggests that judgement or interpretation would not be allowed.

There are other definitions of proxy and observer reports. One definition is that proxy-reported measures include the observer's interpretation or judgement, whereas observer-reported measures are limited to the reporting of observations without judgement or interpretation [5]. A book on patient-reported outcomes cites two factors as distinguishing proxy reports from observer reports: the proxy's perspective-taking and the proxy's contribution of interpretation or judgement to the observation [6]. The Montreal Accord on Patient-Reported Outcomes notes that both observer- and proxy-reported outcomes involve observation by individuals who lack professional training; however, proxies are a "special kind of observer" with a "shared experience" with the patient that facilitates their reporting [7] (p. 122). The statement regarding professional training is used to differentiate observer- and proxy-reported outcomes from clinician-reported outcomes, which involve observation but also clinical judgement by someone with appropriate professional training [7]. However, other authors have indicated that clinicians [6] or people with professional training [8] may be able to provide observer-reported outcomes. The latter approach is used in the International Society for Quality of Life Research (ISOQOL) dictionary definition for observer-reported outcomes.

The many studies that have compared patient and proxy reports for the same individual on the same measure have not excluded clinicians from serving as proxies. Paired or dyad proxy-patient studies for chronic disease have had a range of individuals serving as proxies, including family caregivers, nurses and physicians [9]. Systematic reviews have considered both health-care professionals and significant others as proxy raters [9, 10]. Triad studies have compared reports from patients, clinician proxies and family proxies [11, 12]. In palliative care, measures about patient symptoms or QOL designed for clinician completion are sometimes referred to as proxy measures. For example, the Palliative care Outcome Scale (POS) [13] and its updated version, the Integrated Palliative care Outcome Scale (IPOS) [14] have a self-report and a proxy-report version, and the proxy-report version is designed for staff clinicians to complete. At times, family carers have completed the POS in studies [15, 16].

In general, the term "proxies" as described above tends to refer to someone who completes an assessment, rather than a patient. Proxy reports are the assessment from the proxy. However, proxies may be involved in ways other than completing the assessment. Proxies may also assist the patient in completing the assessment, which is sometimes referred to as proxy assistance. This assistance can range from reading the questions to the patient, writing down the patient's answers or translating the questions and/or answers [17]. Proxy assistance can be one of the response options in health surveys [17, 18]. Proxy and proxy assistance are not necessarily equivalent. Research on proxy assistance is limited in comparison to research on proxy reporting.

18.2.2 Who Can Be a Proxy?

In most dyad studies, non-clinician proxies are family members or other relatives [9, 10, 19–21]. Typically, spouses or partners comprised many of the proxies and in some cases, studies specified

that spouses/partners were to be the proxies [21]. In paediatrics, parents typically serve as proxies [5, 22–24], although other caregivers may also be asked to report [5]. In palliative care, some proxy-specific measures such as the POS [14, 25, 26] are designed for staff (clinician) proxy completion. Other measures that focus on the quality of care at the end of life, or the quality of death and dying tend to be completed by family caregivers [27]. These instruments often include some assessment of patient symptoms [28] and can thus be considered proxy reports if completed by someone other than the patient. Furthermore, these instruments are designed for completion by bereaved relatives or others after the patient has died [29–33] and will be proxy-reported by definition.

18.2.3 Who Should Be a Proxy?

In adult health settings, most concordance studies have been dyad and not triad studies, making comparison across different types of proxy raters difficult. There is no consistent evidence supporting one type of family proxy rater over another, or family raters over non-family raters. Two head-to-head studies using the COOP/WONCA, a generic instrument, and comparing self-reports from patients receiving chemotherapy to proxy reports from significant others and clinicians did not find consistent evidence to support one type of proxy rater over another [34, 35]. However, an assessment comparing self-reports from patients with hepatocellular carcinoma using the FACT-Hep, a disease-specific measure, found that reports from family caregiver proxies better approximated patient reports than reports from physician proxies [12]. In patients with terminal cancer, physician-patient concordance was better than family-patient concordance for some outcomes and worse for others [11]. In one study, there was no consistent difference in concordance for spouse/partner proxies and non-spouse/partner proxies [36]. In another, patient-proxy concordance was greater for spousal proxies compared to other proxy types [37]. Importantly, in both these studies there was only one type of proxy rater per patient, that is, either a spouse or a non-spouse; thus, the results from these studies are not fully comparable to the triad studies. In a population-based survey of patients with cancer, spousal proxies tended to report better mental health scores and care experience for patients compared to other proxy types such as child proxies [38]. This survey had only patient or proxy reports for a given individual and thus proxy-patient concordance could not be assessed.

In non-cancer settings, evidence from concordance and non-concordance studies (i.e. studies where proxies substitute for unavailable patients) suggests that spouses/partners may not always be optimal raters. An evaluation using a nationally representative survey of elderly adults compared the reports of different raters (self-reports in some cases, proxy reports in others) regarding health service use with administrative claims data. Spousal proxies were similar to self-reporters in terms of concordance with claims-based reports of health service use; however, non-spousal proxies as a group had the best concordance [39]. One possibility for these somewhat inconsistent findings is age: given the study's focus on elderly adults, spouses and self-raters are likely to be elderly. A large, prospective cohort study focussing on older women found that partner proxies were less concordant with self-reports of dependency than other proxy types [40]. This may reflect a possible gender effect: most proxies in that study were men, whereas in other evaluations a majority of proxies were women [38].

Furthermore, there is some evidence that factors other than the type of proxy rater may affect how proxies report on adult patients. Patient performance status was an important factor in patient-proxy concordance in head-to-head triad studies, with the best concordance seen among patients with either very good or very poor performance status [34, 35]. A U-shaped relationship has been suggested, with the best concordance seen in at the ends (i.e. very good or very bad status) and the worst in the middle (i.e. moderate status) [34]. Patient-proxy concordance was also found to be higher among patients with worse symptom burden [11]. Findings about the

impact of cognitive difficulties on patient-proxy concordance are inconsistent, with evidence for both better [11] and worse [41] proxy-patient concordance for patients with cognitive difficulties. Worse proxy health and greater proxy caregiving burden were associated with worse proxy-patient concordance, although this was not consistent across studies [21]. Interestingly, there has been some evidence to suggest better dyadic concordance among patients with recurrent cancer [37, 42]. Patient and proxy demographic characteristics have not been consistently associated with concordance [19, 21]. Proxy engagement in patient care was associated with proxy reports of patient care experience and patient mental health [38]. Importantly, the correlation among proxy characteristics such as engagement in care and the type of relationship the proxy had with the patient was moderate at best [38]. It is therefore worthwhile to consider the collection of additional information about proxy raters when proxies are used.

In paediatric research, a parent is often the proxy [22]. A key difference between proxy reporting in adult and paediatric health settings is the important role of parents in health-care decision-making. In particular, parental perception of child health is a factor in health-care use [43, 44]. There have been relatively few studies that have considered differences between parental proxies. In studies that include mothers and fathers as proxies, the majority of the proxies have been mothers [22]. The few studies that have examined differences between maternal and paternal proxies have found some differences, but these studies concluded that in most cases these reports can be used interchangeably [45, 46]. Factors that may affect proxy reporting include child age, with greater proxy-patient discordance seen for older children compared to younger children [47]. Severity of illness was a predictor of proxy-patient concordance; however, its effect appeared to vary by domain [48]. Additionally, treatment status is an important consideration as the association of factors such as gender with concordance differed by whether or not children were on treatment [48].

In palliative care, the type of proxy may depend on the situation. Measures such as the POS were designed for staff/clinician proxy report [26]. The selection of a suitable proxy for reporting on a patient's dying experience has been discussed as a methodological challenge in palliative care [49]. The recommendation for a proxy is someone who is involved in care and who is adequately informed about the patient's experience [49]. Since information about the patient's QOL and quality of care in the final weeks of life are often collected after death, family caregivers are often appropriate proxies [50].

18.2.4 Advantages of Using Proxies

A key advantage of using proxies is that information is collected about patients that would otherwise be missing. This is particularly salient for specific contexts such as palliative care, where completion rates for patient-reported outcome measures may be very low due to patient illness [50]. Furthermore, assessments of the patient's dying experience are generally only measured after death and will therefore require proxy reporting. For paediatric cancer, there may be concerns about the ability of patients to complete outcome measures if they are very young or have cognitive effects from disease and/or therapy [44]. Thus, using proxies can help minimise missing data.

A second, and related, advantage is that proxy use may also minimise selection bias [51]. Patients requiring proxies tend to be in worse health compared to patients able to self-report [17, 52]. They may also differ from patients who are able to self-report in terms of sociodemographic characteristics such as education and income [17, 52]. Exclusion of these patients can therefore result in unrepresentative samples in surveys, or study populations of limited generalisability. Furthermore, the exclusion of these patients means that the estimate of health outcomes does not reflect the experience of the sickest and most vulnerable patients.

Additionally, research on patient-caregiver dyads has demonstrated interdependence

between patient and caregiver health [53]. Dyadic research in married couples where one spouse has cancer identified that changes in patient health affected both patient and spouse symptoms, highlighting the importance of considering the whole dyad [54]. These findings of interdependence suggest that informal caregivers acting as proxies may have some insight regarding patient health.

18.2.5 Disadvantages of Using Proxies

Although using proxies has advantages, it also has disadvantages. The greatest concern regarding proxy reports is that they are not equivalent to patient reports, and their use may introduce bias. Dyad studies that look at paired patient and proxy reports for the same individual have identified discrepancies, often termed proxy bias [9, 10, 19–21, 55]. Generally, the extent of agreement between patients and proxies in dyad studies is good [9, 21]. This refers to both individual-level and group-level agreement. Individual-level concordance is usually assessed through correlation, and group-level concordance is assessed by comparison of a summary statistic such as a mean or median [56]. A recent review of concordance studies in adult cancer identified *t*-tests, Wilcoxon signed-rank tests and comparisons of effect size as methods used for evaluating concordance at the group level [21]. At the individual level, correlation methods employed included intra-class correlation (ICC), Pearson's r and the weighted kappa [21]. Heterogeneity in methods for evaluating concordance has been reported in previous reviews as well [9, 55].

Such heterogeneity is a limitation of the concordance studies that form much of the evidence used to ascertain proxy bias. This evidence also has other significant limitations. Many dyad studies have relatively small samples of ≤50 pairs, and these studies also tend to show worse concordance [9, 10]. Additionally, although some general conclusions such as those regarding the importance of observability can be made, it is important to note that concordance studies have involved a wide variety of outcome measures and methods. This heterogeneity makes comparison across studies and ultimately broad, summary interpretations difficult. Furthermore, interpretations of patient-proxy concordance on instruments should also consider the reliability of the instruments themselves, as well as the range of scores observed on the instruments when assessing concordance [9]. Limited variability in scores may be a particularly salient problem for smaller studies and provide an overly negative picture of concordance [9].

Notwithstanding these limitations, the literature suggests that proxy-patient agreement tends to be better for more observable domains and worse for less observable domains [9, 21, 55]. Similar findings have been reported in paediatric research as well [22]. Proxies tend to underestimate function and QOL [9, 21] and overestimate symptoms [9, 55]. However, for some symptoms such as pain, proxy underestimation of pain has been reported [55]. Proxy-patient concordance was better for physical symptoms compared to psychosocial symptoms [57], which is consistent with other findings regarding observability. Furthermore, concordance has also been found to vary by different aspects of symptom reporting, and specifically was worse for distress compared to severity and frequency [57]. A conceptual measurement model of proxy reporting suggests that the phenomenon of better (i.e. less discordant) proxy reports for more observable domains is because less observable domains require proxy assessment and interpretation of signs related to those constructs [58].

Whether or not proxy-patient concordance changes over time is an important question that has not been particularly well-studied. Just four of the 23 concordance studies that Sneeuw and colleagues assessed in a systematic review looked at concordance at two points in time [9]. It is important to note that other factors may also affect changes in agreement over time. In a concordance study of paediatric patients with cancer, better proxy-patient agreement was seen in the group of patients who were not receiving treatment [48]. Another study in paediatric oncology found better concordance at baseline compared

to follow-up, but it suggested that symptom load could be an explanatory factor [59].

The limited evidence that exists for changes in concordance over time in adult patients is not consistent. In a study of patients with advanced cancer, it improved at the second assessment [60], but this was not the case in a study of patients with brain cancer [41]. There are several possible reasons. One is that the proxy raters in the studies differed; specifically, all the raters in the advanced cancer study were spouses [60], whereas 25% of the raters in the brain cancer study were other relatives. Another is that the advanced cancer study restricted its analysis to pairs with data at both time points, whereas the number of participants included in the analysis in the brain cancer study differed at baseline and follow-up. A study using multilevel models to look at congruence over time found that congruence improved over time for physical function, but not for symptoms [61]. Understanding changes in proxy-patient concordance over time, as well as the other factors that may affect this such as changes in treatment or symptomatology, is an important topic for future research.

Additionally, another important question regarding the use of proxies is if their use changes the outcome. This question is difficult to answer in concordance studies, since even when a proxy is used a patient report is available. The literature is not conclusive on this, and the findings appear to vary by disease area and domain. Proxy bias was estimated to be significant in a nationally representative study of disability, and proxies appeared to underestimate disability for younger individuals but overestimate it for older individuals [62]. However, another study using the same data but focussing on health-related QOL found that the use of proxies had a minimal impact after adjusting for sociodemographic and clinical factors [63]. In a population-based cancer survey, it does not appear that the use of proxies had substantial impact on estimates of care experience and quality [64], or shared decision-making for patients receiving or scheduled for chemotherapy [65]; however, there did appear to be an impact on estimates of health-related QOL [66]. An assessment of health-related QOL in survivors of paediatric central nervous system (CNS) cancers did not find different results by respondent type (parental proxy or self-report) [67]. These findings highlight the importance of considering patient population and outcome when reviewing the concordance literature and planning a study in which proxies may be required. A further consideration is the type of instrument for outcome measurement, which will be discussed in the next sub-section.

18.2.6 What Should the Proxies Report?

Another consideration when evaluating concordance studies and selecting instruments for proxy report is instrument content and the implications of this for proxy report. Even though different instruments assess broadly similar domains, there may be substantial variability in the assessment. For example, although both the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire-Core 30 (EORTC QLQ-C30) and the Functional Assessment of Cancer Therapy-General (FACT-G) are cancer-specific measures with suitable psychometric properties, there are differences in domains as well as phrasing [68]. The EORTC QLQ-C30's physical function domain incorporates aspects such as mobility, including the performance of basic tasks, whereas the FACT-G's physical well-being domain incorporates aspects such as energy [21]. The social domains of the two instruments differ as well [69]. Variability in domain content has also been reported in paediatric measures for which proxy-patient concordance has been evaluated [22]. Given the findings about observability and patient-proxy concordance, phrasing and items are important considerations for researchers when evaluating the evidence about proxy bias on measures and when choosing measures and domains for proxy report. Although instrument choice should be guided by the research question, clinical appropriateness and other important factors, if proxy use can be anticipated then the observability of the items and domains in the measures of interest should be examined.

Another consideration when evaluating concordance studies and possible instruments is that the evidence base for some measures may be stronger than others. In adult cancer, a number of concordance studies in cancer have examined patient-proxy concordance on the EORTC QLQ-C30 [9, 21]. In patients with advanced cancer at the end of life, the McGill Quality of Life (MQOL) tool has been evaluated frequently [21]. The COOP/WONCA charts, which are a generic instrument, also have been evaluated for patient-proxy concordance in a cancer population [65]. In paediatrics, proxy-patient concordance on the Pediatric Quality of Life Inventory™ (PedsQL™) has been evaluated frequently, including in paediatric patients with cancer [24].

18.2.7 How Should Proxies Be Asked to Report?

In addition to instrument content, another important issue is the perspective from which the proxy approaches the question. Pickard and Knight discuss two perspectives by which the proxy may assess the patient when making a report: (1) the proxy-patient perspective, in which the proxy attempts to answer as the patient would and (2) the proxy-proxy perspective, in which they report on the patient from their own point of view [3]. The proxy's report of the patient's QOL may differ depending on the perspective taken, resulting in what Pickard and Knight term the "intra-proxy gap" [3]. There have been several studies that sought to examine how different perspectives may affect proxy bias.

A randomised trial of the impact of the different perspectives on proxy-patient concordance on the EORTC QLQ-C30 did not find evidence for substantial differences in concordance across the two perspectives. The proxy-proxy perspective had significantly better concordance for some functional domains, but the proxy-patient perspective had significantly better concordance for a symptom domain. Generally, however, the different perspectives resulted in similar levels of proxy-patient concordance [70]. A different randomised study assessing the impact of different perspectives on concordance using the Memorial Symptom Assessment Scale (MSAS) had different results. This study considered three prompts: (1) a "neutral" prompt, which did not encourage the adoption of a particular perspective; (2) an "imagine-patient" prompt, which corresponded to a proxy-patient perspective; and (3) an "imagine-self" prompt, which corresponded to a proxy-proxy perspective. Discrepancies were relatively low for the "neutral" prompt, and the "imagine-patient" prompt appeared to be better in terms of concordance than the "imagine-self" prompt for some aspects of the MSAS [71]. Earlier work on this topic had similar findings, in particular that "imagine-patient" appeared to be somewhat better than "imagine-self" but not noticeably better than a "neutral" prompt [72]. A qualitative analysis of caregiver perceptions under different instructions and prompts found that caregivers in the "imagine-patient" prompt and the "neutral" prompt appeared to have similar perceptions and responses, which may help explain the quantitative findings [73]. Interestingly, different prompts appeared to have minimal impact on concordance when proxies already had long-lasting caregiving relationships and strong communication with patients [74], highlighting the importance of considering other factors in addition to perspectives, instructions and wording. A recent study that used hypothetical vignettes to assess potential proxy responses on the ICECAP-A (ICEpop CAPability measure for Adults) measure from members of the public found identified perspective and proxy interpretation of items to be factors that affected proxy responses [75].

18.2.8 What Is a Proxy Measure?

A further consideration for researchers is that the concordance literature focusses primarily on proxy completion of measures developed specifically for patients, that is, patient-reported outcome measures (PROMs). This may be a result of the use of proxies as substitutes for otherwise missing patient responses. For adult populations, outside of dementia and

palliative care settings there have been relatively few measures developed de novo for proxy use, rather than designed for patient use and subsequently adapted for proxy use. The term "proxy measure" may also refer to an informant measure, since these terms are sometimes used interchangeably. For example, Gruber-Baldini and colleagues consider the terms informant and proxy to be equivalent [51]. Grill and colleagues note that informant measures cover diverse areas, including "patients' cognitive domains, neuropsychiatric symptoms, occupational and community activities, and basic and instrumental activities of daily living" [76] (p. 243).

Another complexity is distinguishing between observer-reported measures and proxy-reported measures, as discussed previously. The use of different definitions further complicates this issue. The definition of informant measures provided by Grill above could arguably refer to either proxy or observer measures, depending on what is being assessed. In general, however, it appears that the term "informant" is considered to be the same as "proxy" [77–79]. The term "informant" appears to be used more commonly in dementia and in relation to assessments in dementia.

In palliative care, as noted above there are measures that have been designed specifically for proxy use. Some measures are designed only for proxy completion and some have both proxy and patient versions. For example, the POS [13] and its updated versions such as the IPOS [14] have both patient- and proxy-reported versions, where the proxy version is designed for staff/clinician report. However, measures that focus on end-of-life care such as the Quality of Death and Dying (QODD) or the Good Death Inventory (GDI) [29] are only for proxy report.

In contrast, in paediatrics some measures may have both patient and proxy versions and some, particularly those for very young children, may have only proxy versions. For older children, a proxy version may be available but where possible the self-report version would be recommended for use.

18.3 A Closer Look: Proxy Assessment in Brain Cancer

Brain tumours and their treatments negatively affect cognition and cognitive abilities [80] (see also Chap. 24, this volume). Proxy reporting is therefore a consideration in brain cancer. Previous research in this area has included the evaluation of patient-proxy concordance on PROMs including the FACT brain cancer module, FACT-Br [81] and the EORTC QLQ-C30 [41, 82] and the brain cancer-specific QLQ-BN20 module [82]. Generally, patient-proxy concordance on QOL measures is reasonable [41, 81, 82], although it is concerning that patient-proxy concordance appears to be better when patients are less cognitively impaired [41, 81]. The development of new measures for this population, or for patients with brain metastases, has also involved the development of proxy versions. Zil and colleagues developed a disease-specific, multidimensional QOL instrument for patients with anterior skull base tumours [83, 84] and subsequently evaluated proxy-patient concordance, concluding that proxies could be used to report on patient QOL [42]. Similarly, Agar and colleagues adapted the Dexamethasone Symptom Questionnaire to a version addressing chronic effects for patients with brain tumours or metastases and created a proxy version [85]. Proxy-patient concordance was acceptable and it was suggested that proxies complete the proxy version of the measure when patients could not self-report [85]. Finally, Steinmann and colleagues developed and evaluated the brain cancer-specific DEGRO Brain Module proxy measure and used this instrument in a study of QOL for patients with brain metastases receiving radiotherapy [86, 87].

18.3.1 A Closer Look: Proxy Assessment of Utilities

Health state utilities (HSU or utility) are a measure of QOL measured between 0 (where 0 is anchored at death) and 1 (where 1 is the rating for perfect health) [88–90] (see also Chap. 15, this volume). A utility can be derived from the

patient- or proxy-reported responses to a multi-attribute utility instrument's (MAUI) questionnaire via the MAUI's specific algorithm, also called the indirect method of utility derivation. This is the most common form for deriving utilities, although direct methods such as the time trade-off or standard gamble are also used [89]. Proxy reporting for MAUIs has been used in adult cancer care, albeit infrequently. This is in contrast to other disease contexts in adults such as stroke [91] and dementia [92]. Pickard and colleagues evaluated patient and proxy concordance on the most commonly used MAUI, the EQ-5D, for patients with prostate cancer. Patient-proxy concordance as assessed by intraclass correlation coefficients was reasonable [93]. Consistent with research, concordance was better for more observable dimensions of QOL such as mobility compared to less observable dimensions such as anxiety [93].

In paediatric cancer care, proxy reporting on utility instruments is more frequent. In a recent systematic review of health utilities in paediatric acute lymphoblastic leukaemia (ALL), all studies conducted during treatment used proxy reports only and studies in survivors often used both proxy and patient reports or proxy reports alone [94]. The review focused on the Health Utilities Index Mark 2 and 3 (HUI2 and HUI3) MAUIs. The HUI developers' published guidelines on the HUI mention age-based guidelines for self- and proxy-assessment for self-administered questionnaires. Proxy report alone is recommended for ages 5–12, and proxy and self-report are recommended after the age of 12 [95].

An assessment of proxy-patient concordance in survivors of childhood cancer and controls using the HUI3 found better concordance for more observable attributes, and parents had better concordance with children compared to other types of proxies such as physicians or teachers [96]. A study evaluating oncology nurse completion of the HUI3 for paediatric patients with ALL found frequent "don't know" responses [97]. These findings underscore the importance of considering proxy characteristics when planning to utilise proxy reports.

18.3.2 A Closer Look: Proxy Assessment in Palliative and End-of-Life Care

Proxy reporting is an important consideration in palliative and end-of-life care. Patient deterioration and concern about patient burden represent barriers to research in palliative and end-of-life care, with the use of proxies suggested as a way to ameliorate both of these issues [98]. In general, proxies may be asked to complete measures about patient QOL, resulting in datasets with both self-reports for some patients and proxy reports for other patients. In an assessment of patient symptoms in Australian palliative care through the Palliative Care Outcomes Collaboration (PCOC), less than half of included patients were able to self-report and proxies were used for 51% of patients [99]. If quality of care is assessed, then this is often done by proxy report only, as it is completed after the patient has died. These retrospective reports often include both family perception of their own experience with clinicians and others treating the dying patient, which would not be a proxy outcome, as well as proxy outcomes relating to patient symptoms. Examples of measures that include family reports both as proxy and as a self-report include the Consumer Assessment of Healthcare Providers and Systems (CAHPS) Hospice survey [100] and a mortality follow-back survey [101]. The QODD likewise includes both family perception of patient symptom management and the family's own experience with the health-care team [30].

Proxies are discussed in the Methods Of Researching End of life Care (MORECare) project developed the MORECare statement, which provides best practice guidance for research in end-of-life care. The statement highlighted the expectation of missing data and patient attrition in end-of-life research, and said that proxy ratings from either family carers or staff could be used "where appropriate" [102] (p. 8). The MORECare checklist suggests estimating the anticipated extent of missing data and using this to inform data collection plans for proxy-reported data [102]. In the MORECare International Consensus Workshop, participants agreed that

patient-reported data was prioritised, but the nature of end-of-life care and patient deterioration meant that proxies would be part of end-of-life care research and outcome assessment [103]. Areas of need for future work included analytic methods for proxy-reported data and better understanding of factors that may affect proxy bias [103].

Because of the important role that proxies play in this area of research, choosing a proxy respondent is a key consideration for researchers in this field. One challenge is that there may be multiple caregivers attending to the patient in their last days of life, and thus no one caregiver may be best positioned to serve as a proxy respondent [49]. A possible solution is to collect data from multiple proxy sources [49]; however, this may also produce analytic challenges.

18.3.3 A Closer Look: Proxy Assessment in Paediatrics

Evaluations in paediatric oncology often use parent proxy reports. A systematic review of QOL in children receiving treatment for ALL found that only one of 22 studies used patient self-report alone. Of the 21 studies relying on proxy report, just six also included self-reports from patients [104]. However, nearly half (46%) of studies of paediatric CNS survivors included both self- and proxy-reported assessments, and relatively few (11%) relied only on parent proxy report [67]. At times, proxy assistance may be used: a study of long-term survivors of paediatric brain tumours allowed parents to assist in questionnaire completion if survivors were unable to read or comprehend the items [105]. The proxy issue is an important consideration in the assessment of paediatric QOL [106, 107]. In general, where possible child self-report should be used; however, for very young children or those with significant developmental or other disabilities, a parental proxy report may be the only option [106, 107]. Obtaining results from both parents and children has been suggested [106, 107], although this potentially expensive approach may not be practical in all or many situations.

The International Society for Pharmacoeconomics and Outcomes Research (ISPOR) Good Research Practices For the Assessment of Children and Adolescents Task Force emphasises collecting child self-report where appropriate based on age and child ability to complete such measures, and using informant measures that focus on observable domains if child self-report cannot be obtained [5]. Four broad age groups were considered: <5 years of age, 5–7 years of age, 8–11 years of age and 12–18 years of age. Self-report was seen as optimal for the oldest age group and the most questionable due to lack of evidence regarding the reliability and validity of self-report measures for the youngest age group [5]. Another consideration is ability to interpret and respond to item content; for example, questions regarding the ability of children to comprehend the terminology used for some of the items in the Perceived Stress Scale – 10 (PSS-10) means that self-report is not recommended for children under the age of 12 [108]. Having both self- and proxy-report versions of instruments is recommended for PROMs in routine care [109] or research [110] in paediatrics.

The US National Institutes of Health (NIH)'s Patient Reported Outcomes Measurement Information System (PROMIS®) has both self-report and parent-proxy report versions for paediatric outcome measures. PROMIS® has self-report item banks across multiple QOL domains for children aged 8–17 years of age [111]. Although self-report is prioritised, parent proxy-report item banks have been developed for this same age group to facilitate the collection of QOL data from paediatric patients unable to self-report [112]. PROMIS® parent proxy-report item banks have been assessed in younger age groups as well, such as children aged 5–7 years [113, 114]. When PROMIS® paediatric measures have been translated and validated in other countries, both self-report and parent proxy-report versions have been included in the translation and validation [115].

Another example is the Pediatric Quality of Life and Evaluation of Symptoms Technology (PediQUEST) randomised controlled trial, which

evaluated if feeding back information from PROs to paediatric patients with cancer and their families improved symptom distress and QOL [116]. As the study recruited children aged 2 years or older, decision-making regarding parental proxy report was required. Parent proxy-report was used for children 2–4 years of age and proxy versions of measures were used if children could not complete measures [116]. In a review of generic multidimensional PROMs for paediatrics, more than half of the PROMs had both self- and proxy-report versions, and the instruments with proxy versions only tended to be for very young children [117]. Development of new instruments for very young children seems to follow this pattern: an item bank for children ages 0–3 is for proxy report only [118].

Finally, the KLIK web portal in the Netherlands (https://www.hetklikt.nu/) is an example of the integration of PROMs in routine paediatric care, with both self- and proxy-report versions and decisions on using proxies as the sole reporter based on age. Among the instruments included in KLIK was the PedsQL instrument, which was chosen in part due to the availability of both self- and proxy-report versions [119]. Children 8 and older completed the self-report version of PedsQL and parents reported on behalf of children aged 6–7 using the parent proxy version of the PedsQL [120]. For children aged 5 years and younger, QOL was wholly proxy-reported using a generic multidimensional measure for QOL, the Dutch Preschool Children Quality of Life (TAPQOL) measure [120]. The use of QOL measures in paediatric oncology in clinical practice was evaluated through the Quality of Life in Childhood Oncology (QLIC-ON) intervention, the development and implementation of which has been described previously [121]. In QLIC-ON, the generic measures were completed as described and the answers summarised in a QLIC-ON PROfile that was made available to the oncologist [122]. QLIC-ON demonstrated that this was a helpful and feasible intervention [122]. It was also viewed positively by parents and paediatric oncologists [123]. Capturing QOL through KLIK in juvenile idiopathic arthritis was also successful [120]. Currently, KLIK uses the generic measures described previously and also has disease-specific measures available for specific patient groups [124]. KLIK is integrated into paediatric care, including oncology care, in several Dutch hospitals [125].

18.3.4 A Closer Look: Proxy Assessment in Health Surveys

Surveys of patients with cancer, either as part of broader health or population surveys or surveys that focus on patients with cancer, have often involved proxy reporting. The issue of proxy reporting is one that comes up frequently in the literature regarding survey methodology [126, 127]. Proxies have been asked to report about patient health in surveys in several countries. Examples include the 2013 National Health Service Survey (NHSS) in China [128], the 2011 National Health Service (NHS) adult inpatient survey [18] and the Adult Social Care Survey [129] in the UK, a national adult inpatient survey in Norway [130] and numerous US surveys including the Medicare Health Outcomes Survey (MHOS) [131] and the CAHPS [17] surveys.

There are several surveys that focus on patients with cancer or cancer survivors and use proxies. These include the linked Surveillance, Epidemiology and End Results (SEER) SEER-CAHPS [132] and SEER-MHOS [133] surveys. SEER-CAHPS allows for both proxy assistance and full proxy report [132]. A recent analysis using SEER-CAHPS data to look at timeliness of care for older cancer patients reported that 13% of responses were from proxies [134]. In SEER-CAHPS, proxy respondents provided information about patients' experience with cancer care as well as information about patient health status. Health status is often included as an adjustment variable in models that seek to adjust for other factors when evaluating care experience or quality [135], because health status is known to affect how patients report about their care [136]. Another example of a study of the QOL and care experience of patients with cancer is the Cancer Care Outcomes Research and Surveillance (CanCORS) consortium, which

assessed these and other issues for approximately 10,000 patients with incident lung or colorectal cancer in the USA [137]. CanCORS allowed for the use of proxies in two ways: (1) proxies reported on behalf of a patient with cancer who was alive at the time of contact, but unable to self-report and (2) proxies reported on behalf of a patient with cancer who was already deceased at the time of contact [138]. Having proxies report on behalf of already deceased patients has also been used in another survey evaluating the experience of patients with cancer who received chemotherapy [139]. In CanCORS, differences between proxy and patient report with regard to care experience and quality [64] and treatment decision-making for chemotherapy [65] were small, but this was not the case for QOL [66]. These large QOL differences were seen for both physical and mental health in CanCORS [66]. QOL in CanCORS was assessed by the Short Form-12 (SF-12) generic survey, which has two summary scores: the Mental Component Summary score (MCS) and Physical Component Summary score (PCS) [140]. In the SF-12, all domains are used in the calculation of each score, albeit with different weights depending on the summary score being calculated [141]. This may be one reason why the differences between proxy- and patient-reported scores in CanCORS for both the MCS and PCS were similar.

In both CanCORS and SEER-CAHPS, proxy reports were used for both the outcome variable and adjustment variables. The issue of a proxy-reported adjustment variable is not one that has been considered in detail in the literature on proxy-patient concordance, or even in the methodological literature about approaches for analysing data with proxy reports [51].

18.4 Considerations for Proxy Use: Researchers

18.4.1 Analysis

Analysing proxy-reported data can be challenging. In some datasets, such as those where only proxies report because all patients have died, the analytic methods are more straightforward. Although concerns about errors in proxy report remain, there will be no differences by sites, facilities or groups. However, in "mixed" datasets where some patients self-report and proxies report on behalf of other patients, there are different analytic challenges and concerns when planning and conducting analyses. This section will focus on the methods and challenges for "mixed" datasets.

A standard and so-called "best practice" approach is to use an indicator variable for respondent type in a model that adjusts for other factors that may affect the outcome of interest [142]. This approach has limitations if a study includes both proxy assistance and full proxy report [142], and if there are systematic differences between patients who self-report and those who require proxies [17]. Several researchers have used propensity score methods to account for the systematic differences between proxies and patients [17, 18, 52, 130, 131]. However, these methods have limitations and at a minimum a careful sensitivity analysis is required [143].

To date, there has been comparatively little research on the issue of how best to analyse proxy data, particularly in comparison to the amount of effort expended on concordance analyses. Huang et al. proposed a method in the context of randomised trials [144]. Shardell and colleagues proposed a method in the context of epidemiologic research, with an emphasis on exposure and outcome data, as well as a sensitivity analysis [145–147]. Finally, Hosseini and colleagues discussed the use of a weighted approach for proxy-reported data [148]. All the methods discussed are fairly complex and seeking expert statistical advice is recommended.

18.4.2 Data Collection

In many surveys and studies, relatively limited information about proxies themselves is collected [21, 38]. However, proxy-specific factors such as their relationship with the patient and their engagement in care [38] can affect how proxies report. This points to the importance of collecting data about the proxy as well as the patient when using proxy reports.

18.5 Considerations for Proxy Use: Clinicians

Incorporating PRO data into routine oncology practice can improve communication [149] and may have clinical benefit [150]. Plans for situations where patients cannot self-report should be considered when planning to collect PROs in oncology practice. These situations may include both proxy assistance and full proxy report. For example, patients who do not speak or are not confident in the dominant language of the country in which they reside may rely on family members for interpretation [151]. This may extend to PROMs as well. In paediatric oncology practice, there are guidelines for the use of self-reports and proxy reports at different ages and developmental stages, and proxy versions of patient measures can be kept on hand for older children who cannot self-report. When relying on family members to serve as proxies, clinicians should consider the proxy's relationship with the patient and other proxy characteristics.

18.6 Considerations and Future Directions for Researchers

There has been substantial research on proxy-patient concordance, but there are also areas in which further research is needed. Further research in both methodological and non-methodological aspects of proxy reporting would be beneficial. In the area of methodological research, there is a need to understand what methods are best for analysing proxy-reported data, and developing novel methods for such data if required. There has been relatively little work that examines proxy characteristics and proxy-specific factors that can affect proxy report, particularly over time. Such work could ultimately inform inclusion/exclusion criteria for proxies in studies. Furthermore, in contexts such as palliative care and brain cancer, where high need for and use of proxies can be anticipated, questions around when to switch to proxy reports and how to select the best proxy are important.

Another under-researched area is proxy assistance. Information on this is rarely collected and how best to analyse such data has not been explored. Collecting more data on what proxy assistance may entail in different studies, and how much to allow depending on study requirements, is an important area for future research.

18.7 Conclusion

The use of proxies to assess quality of life in cancer has several advantages as well as drawbacks. Furthermore, proxies clearly play an important role in some areas of cancer care, particularly paediatric oncology and brain cancer. Proxy reports are also used in health surveys that include patients affected by cancer. The advantages of proxy use include the ability to include participants who would otherwise be excluded due to their inability to self-report, and the minimisation of otherwise missing data. The disadvantages include differences between proxy report and patient self-report and the challenges of analysing data that contain information from both patients who cannot self-report and thus have proxy reporters, and other patients who are able to self-report. The key considerations outlined in this chapter should be considered by researchers and clinicians when seeking to collect data in situations where proxy use can be anticipated.

18.8 Questions That Can Be Used for Learning/Testing

1. Who can be a proxy?
2. What are the advantages of using proxies?
3. What are the disadvantages of using proxies?
4. When and how should proxies be used in paediatric oncology care?

18.9 A Topic for Discussion That Can Be Used for Teaching

Proxy measures are used in many aspects of health research and care. In which areas are proxies an important consideration? What is known about proxy measures and proxies in those areas?

18.10 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

Systematic Reviews of Concordance Studies

- Roydhouse JK, Wilson IB. Systematic review of caregiver responses for patient health-related quality of life in adult cancer care. Qual Life Res. 2017;26:1925–54.

This article systematically reviews concordance studies for health-related quality of life in adult cancer, and makes recommendations for disease-specific, generic, and end-of-life specific instruments.

- Sneeuw KCA, Sprangers MAG, Aaronson NK. The role of health care providers and significant others in evaluating the quality of life of patients with chronic disease. J Clin Epidemiol. 2002;55:1130–43.

This article systematically reviews concordance studies for common multidimensional instruments for assessing health-related quality of life.

- Lobchuk MM, Degner LF. Patients with cancer and next-of-kin response comparability on physical and psychological symptom well-being. Cancer Nurs. 2002;25(5):358–74.

This article reviews concordance studies for patients with cancer, focusing on symptoms and quality of life.

- Tang ST, McCorkle F. Use of family proxies in quality of life research for cancer patients at the end of life: a literature review. Cancer Invest. 2002;20:1086–104.

This article reviews concordance studies for patients with terminal cancer, focusing on the end of life.

Conceptual Discussions of Proxy Reporting

- Snow AL, Cook KF, Lin P-S, Morgan RO, Magaziner J. Proxies and other external raters: methodological considerations. Health Serv Res. 2005;40:1676–93.

This article presents a measurement model for proxy data and discusses considerations for proxy reporting.

- Pickard AS, Knight SJ. Proxy evaluation of health-related quality of life: a conceptual framework for understanding multiple proxy perspectives. Med Care. 2005;43:493–9.

This article presents a conceptual framework for proxy perspectives and considers how proxy perspectives can affect proxy reporting.

Considerations for Proxy Reporting in Paediatric Studies

- Matza LS, Swensen AR, Flood EM, Secnik K, Leidy NK. Assessment of health-related quality of life in children: a review of conceptual, methodological, and regulatory issues. Value Health. 2004;7:79–92.

This article discusses the advantages and disadvantages of proxy reporting in paediatric health contexts.

- Matza LS, Patrick DL, Riley AW, Alexander JJ, Rajmil L, Pleil AM, Bullinger M. Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force. Value Health. 2013;16:461–79.

This article presents good research practices for patient-reported outcome assessment in children, including age- and developmentally based guidelines for the use of proxy and self-report measures.

18.11 Research in Context

Snow et al.'s paper about proxies published in *Health Services Research* in 2005 was an important paper in the field. It was one of the first to introduce a conceptual framework regarding proxy use and to consider proxies within the broader framework of "external raters". The paper differentiated proxies from "other raters" in that proxies are filling in an otherwise missing patient report, rather than providing complementary information to supplement an existing patient report. The paper considered multiple issues in the conceptual framework, including data collection, the definition of bias, and analysis. This work highlighted that the observability of the outcome is an important consideration for proxy reports, in that bias is likely to be lower for such outcomes.
Snow et al. [*58*].

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2. Food and Drug Administration. Guidance for industry: patient-reported outcome measures: use in medical product development to support labeling claims. Silver Spring, MD: US Food and Drug Administration;2009. https://www.fda.gov/media/77832/download. Accessed 1 December 2020.
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19 The Role of Psychologists and Psychological Approaches in Cancer Care

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Contents

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19.1 Introduction

Over the past 70 years, empirical evidence on oncology signified that cancer exerts a significant psychological impact on both patients and family members with regard to mental health [1–3], often leading to feelings of uncertainty concerning the course of the disease, prognosis, survival rates, and health-related quality of life [4]. Research has demonstrated that 35–40% of cancer patients meet criteria for a psychiatric disorder diagnosis (i.e., depressive disorders, anxiety disorders, trauma-/stress-related disorders, somatization and somatic-symptom disorders, sexual disorders and dysfunctions, neurocognitive disorders) [5–8]. The burden of living with cancer is even higher for advanced stage patients and in contexts of palliative care, compared to cancer survivors [9, 10]. Additional hindering psychosocial and existential difficulties, such as loss of meaning, health anxiety, existential distress, and demoralization are present in 15–20% of cancer patients [11]. Psychological distress may result in lower survival rates and more elevated mortality rates in cancer patients [12]. In addition to this, patients face an additional burden as everyday routine tasks become hard to complete and there is considerable compromise in health-related quality of life [13].

Based on the World Health Organization (WHO), health-related quality of life encompasses the mental, emotional, and physical domains as well as the cognitive, social, sexual, and spiritual functionality of the person [14]. Health-related quality of life focuses attention on quality of life that is associated with and influenced by health or the absence of health [15]. Mental health and health-related quality of life are not synonymous, yet they are related. Female breast cancer patients who report more depressive symptoms also report poorer health-related quality of life [16]. Specifically, the total depression score in this study was negatively correlated with social functioning, mental functioning, physical functioning, general health, gastrointestinal symptoms, and the total Functional Living Index-Cancer [16]. Similarly, individuals with urgency urinary incontinence combined with stress urinary incontinence or urgency urinary incontinence plus other incontinence experience greater mental health difficulties and more deteriorated health-related quality of life [17]. Consistent with the aforementioned studies, mental health difficulties (i.e., internalizing and externalizing problems) are shown to be strongly correlated with health-related quality of life even in young individuals (8- to 13-year-old children) [18]. Given the link between mental health and health-related quality of life, this chapter will be referring to both concepts.

Psychologists who work within oncology settings aim to improve the health-related quality of life of cancer patients and their caregivers or significant others through their multifaceted roles in cancer care and via the delivery of empirically supported psychological interventions. Given the high risk of psychopathology and deteriorated quality of life in cancer patients, this chapter aims to familiarize readers with: a) the role of psychologists in cancer care; b) available empirically supported psychological interventions for improving quality of life, functionality, and vitality in living in cancer patients and their support networks; and c) self-care practices for psychologists.

19.2 The Role of Psychologists in Cancer Care

The Council of the European Union (2008) has emphasized that to accomplish optimal outcomes in routine cancer care, "a patient-centred comprehensive interdisciplinary approach and optimal psycho-social care should be implemented," in addition to "rehabilitation and post-treatment follow-up for all cancer patients" [19, par. 5, p. 2]. Also, the council has encouraged countries to take into consideration "the psycho-social needs of patients and improve the quality of life for cancer patients through support, rehabilitation and palliative care" [19, par 19, p. 4]. Addressing psychological needs must be incorporated into the practices, policies, and standards of healthcare systems of all European and International countries, which must be designed

to ensure the delivery of psychological services to all patients who need psychological support [20, p. 8-9]. According to a special issue of the American Psychological Association, psychology and evidence-based practice constitute considerable contributions in addressing the persistent needs of individuals with cancer [21]. Psychology is also considered as a hub science as it is related to many other sciences and supports people in learning to change unhealthy behaviors that can cause cancer and increase healthy behaviors that enhance the quality of life of individuals who are living with cancer or are cancer survivors [21].

The role of psychologists in cancer care is encapsulated in the following quote by Viktor E. Frankl in his book *Man's Search for Meaning*: "The meaning of life always changes, but... it never ceases to be . . . we can discover this meaning in life in three different ways by: (1) creating a work or doing a deed; (2) experiencing something or encountering someone; and (3) the attitude we take toward unavoidable suffering" [22, p. 115]. This accentuates that psychologists working in cancer care, through their collective actions, can provide support to patients, caregivers, relatives, and the interdisciplinary team they belong to: by helping them in establishing meaning and encouraging values-based actions and continued living even in the course of suffering. According to Kasl-Godley and colleagues (2014), high-quality care to cancer patients can be achieved by adopting a palliative care viewpoint, within which the psychologist plays a significant role in helping patients and significant others deal with the psychosocial, spiritual, and other quality-of-life challenges that arise as a result of cancer [23].

A palliative care viewpoint denotes to the care that is offered at any period during the path of the disease, which aims to decrease physical as well as psycho-social-spiritual suffering, ameliorate quality of life, successfully manage symptoms, and provide holistic, interdisciplinary support both to the patient and relatives/significant others in every part of the course of the disease, irrespective of the stage of illness [24, 25]. Specialized palliative care refers to the specialist training specialist clinicians undertake in addition to the certification for palliative care as a novel medical discipline, whereas basic palliative care encompasses basic care and symptom control offered by individuals who are not palliative care specialists (i.e., oncologists, general physicians who did not receive such training) [26]. It is preferable that such an approach to care starts early from the time the patient receives a diagnosis of a life-menacing disease such as cancer and can be offered simultaneously with other treatments which are curative or are used to extend life [23]. A recent systematic review and meta-analysis of advanced cancer patients has demonstrated that specialized palliative care reduces patients' suffering and ameliorates satisfaction and health-related quality of life, including symptoms such as nausea, pain, fatigue, and psychological and physical functioning and to a lesser extent spiritual and social functioning [27]. Two randomized clinical trials have even demonstrated improvement in survival [28, 29]. These findings accentuate the importance of incorporating specialized palliative care early in the course of the disease, particularly for advanced cancer patients. The study by Temel and colleagues (2010) in patients with metastatic non–small-cell lung cancer also supports early palliative care provision [29]. In this study, early palliative care resulted in substantial ameliorations in both quality of life and mood at 12 weeks compared to patients who received standard care. Also, patients receiving early palliative care had more prolonged survival and experienced less aggressive care at the end of life [29]. Adopting such a viewpoint from the beginning allows for an easier transition should the treatment(s) directed at the disease cease to be effective. The most important focus of a specialized palliative care approach is to enhance the health-related quality of life of cancer patients, which can positively affect the trajectory of the disease, aid patients and significant others in making difficult decisions, and prolong life [29]. Additionally, palliative care entails end-of-life care, which can include referring the patient to a specialized hospital or hospice unit, and provision of support to family and significant others throughout the bereavement phase [30].

Psychologists play an important role in assessment and provision of psychological support for cancer patients and their families, in crisis intervention, and as health experts in cancer care within an oncological multidisciplinary team. Psychologists working within cancer care acquire sufficient and necessary knowledge and expertise in effective psychotherapeutic approaches for this population and contexts. Additionally, their role entails managing the dynamics of the interdisciplinary team and conducting research and contributing to policy and practice guidelines. Health professionals working within oncology including psychologists may be at risk for burnout or stress; thus, self-care practices for psychologists are fundamental for themselves and also for training their co-workers in such practices. Specific areas of function of psychologists within oncology settings are discussed next.

19.2.1 Assessment, Psychological Support, and Therapy for Patients and Their Families

Psychologists devote the majority of their time in direct psychological support for patients and family members [31]. The process of care begins with assessment aimed at identifying the patients' and their caregivers' difficulties and needs. Particular attention is paid as to how cancer is regarded by the patient, how it has affected their life and well-being, changes made in health-related behaviors and concerns, or fears experienced about the future. Subsequently, psychologists conduct a thorough, individualized functional analysis and case conceptualization. This case conceptualization guides the intervention targets and the psychotherapeutic approach to be adopted for the particular patient with their set of needs. A characteristic of this approach is that the effects of intervention(s) are constantly assessed, and re-conceptualizations and adjustments are made along the way. This dynamic assessment-delivery of intervention interplay is particularly helpful and of great importance when psychologists have very little time (maybe even just one session) with a particular patient [31].

During the assessment, ideally information is collected from a multitude of sources, from the patients directly, their families, caregivers, and significant others, as well as from other medical and health professionals. Assessments should be multilevel and can include the following: (a) clinical interviews; (b) standardized self-report measures, such as the Hospital Anxiety and Depression Scale [32] and the Brief Symptoms Rating Scale [33]; (c) collecting information from various sources regarding current difficulties and concerns, psychological symptoms (i.e., anxiety, insomnia), physical symptoms (i.e., pain), level of functioning, level of awareness about the diagnosis and disease progression, perceptions of the disease, of medical therapy, of suffering, of the future, and of death and what the patient knows regarding the diagnosis [31]. Additional information is also gathered about emotional reactions, pleasurable (i.e., feeling grateful) and difficult feelings (i.e., helplessness) of patients and their families, their coping strategies, their psychological flexibility and self-care practices, habits, and interests. It is important to also assess the support system of the patient, such as his/her relationship with relatives and caregivers, and the family's cohesion and functioning as well as the ways the family responds emotionally (i.e., blaming the patient, self-blaming, grief) [31]; and the doctor-patient relationship. It is vital to also assess any unfinished business within the family, the family's dynamics, and whether there are any difficulties or needs relating to children (i.e., how to break the bad news to a child, separation anxiety, grief).

Furthermore, during the assessment it is important for psychologists to have the capacity to detect and distinguish normal grief and complicated or prolonged grief [34]. They need to have knowledge regarding how to educate and provide support to individuals experiencing normative grief and wishing to receive therapy as well as provide referrals to other healthcare professionals (i.e., psychiatrist) when complications like active suicidal ideation with high risk are detected in bereavement [35]. Feelings of helplessness, hopelessness, guilt or worthlessness and pain constitute indicators for assessing the risk of

suicide. Severe depressive symptoms tend to precede more severe postsurgical pain which in turn can exacerbate depression [36, 37]. It is pertinent that the psychologist can distinguish between passive suicidal ideation ("I wish I did not wake up tomorrow morning") and active suicidal ideation ("I wish I do not wake up tomorrow morning and this is how I will make it happen") [38]. A death wish must not necessarily be regarded as a wish for euthanasia, but as an indicator of extreme suffering and a cry for help, which needs to be explored further. The psychologist must be able to conduct a risk assessment, including risk and protective factors, and make a safety plan in collaboration with the patient according to the patient's risk level of committing suicide.

Psychologists also need to acknowledge that patients experience a variety of losses as a result of cancer and medical treatments. They experience losses in their functioning, their health (may even lose aspects of their body such as their hair), their autonomy, their role in the family, their hopes and desires, and losses in their sense of belonging and "normalcy," which lead to feeling that their sense of identity is endangered [23, 39]. It is paramount that psychologists help patients, and their caregivers explore the effect and the meaning of expected or current losses, which can lead to creating new meaning [38]. New meaning cannot be forged and not all patients will find meaning in the process, yet even sharing the experiences of loss and feelings related to loss with a caring psychologist may reduce the loneliness of the experience [23]. Also, it is proposed that psychologists also gradually learn and acquire sufficient experience to endure and tolerate the presence of a dying individual as well as be capable of comforting significant others, addressing concerns and fears and correcting misconceptions [23].

Psychological therapy (individual or family) is integrated within this assessment-therapy loop and is individualized and provided according to the needs of each patient and oriented toward improving functioning and quality of life. Psychological support or therapy can be flexibly offered in inpatient or outpatient settings or offered in homecare by psychologists working in synergy with other interdisciplinary team members, such as physicians, nurses, social workers, and physiotherapists [40]. The assessment-therapy process is a continuous sequence of evaluating outcomes and modifying therapy dynamically as patient needs or context change. Bereavement and grief counseling can also be provided to family members, caregivers, and significant others [31]. Thus, psychologists help patients from the outset of the first symptoms of a problem, to diagnosis and throughout treatment and recovery or the dying process, and can continue to work with bereaved significant others in the case of a patient's death. For recovered patients, psychologists may follow up the patient for a period of time to help with adjustment and re-entry into life, the workforce, duties, etc. Fear of recurrence and stress around future appointments, tests, or other procedures are a common concern. Also, with the advent of pharmacotherapy, numerous individuals may need to take prophylactic, adjuvant, or other medication long term; hence, issues of adherence and managing side effects are also important for psychologists to be aware and address.

The main psychosocial concerns cancer survivors encounter are anxiety and fear of cancer recurrence, depression, and sexual intimacy changes [41]. Also, cancer patients may encounter existential and spiritual distress, feelings of hopelessness, guilt, regret, remorse, sadness, grief, have questions regarding meaning, and a sense of unfinished business [42]. These concerns tend to constitute unmet needs that impact heavily upon the individuals' quality of life. It is paramount that psychologists address these and particularly fear of cancer recurrence, sexual-related worries, as well as spiritual and religious beliefs and concerns, which are discussed in the following section. Other unmet needs, such as providing culturally sensitive healthcare and addressing physical and/or psychological difficulties cancer patients tend to refrain from reporting are also discussed.

19.2.1.1 Addressing Typical Unmet Needs That Impact Quality of Life

Addressing Patients' Fear of Cancer Recurrence Fear of cancer recurrence is experienced by all cancer patients and it impacts quality of life, healthcare use of services, and adherence to follow-up examinations and medications [43]. It is the most commonly reported unmet need in cancer survivors [44]. Fear of cancer recurrence is the worry or fear of cancer returning or progressing to the same or another body part or organ [45]. Though it is completely normal and understandable to fear recurrence, moderate to high level of fear of cancer recurrence (clinical level) exists in 42% of mixed cancer diagnoses survivors and up to 70% in vulnerable cancer populations, like younger breast cancer survivors [46, 47]. According to a systematic review that included fear of cancer recurrence studies, individuals who are most vulnerable to encountering fear of recurrence are those who are newly diagnosed with cancer, younger survivors, those experiencing severe side effects, anxiety disorders, and more elevated subjective perception of risk [48]. Younger individuals do not expect a diagnosis of cancer, and a cancer diagnosis can be experienced as menacing to living in line with important life values such as having children or career prospects [48]. Additionally, individuals who experienced past traumatic events associated with uncertainty and cancer (i.e., family members dying from cancer), anxiety disorders, and side effects reminding them of cancer tend to be more vulnerable to fear of cancer recurrence [49]. It is important to identify cancer survivors who exhibit clinical levels of fear of cancer recurrence in order to address it and alleviate its adverse effects on psychological well-being [44]. Despite the common occurrence of fear of recurrence, patients exhibiting elevated levels of fear are not usually referred to a psychologist nor do they receive help in this area [44]. Psychologists can help make other professionals aware of fear of cancer recurrence and its impact on patients' quality of life and train them to assess for it and refer for therapy to psychologists specialized in working with oncology patients. Psychologists can then design and implement fear of cancer recurrence empirically validated interventions.

Addressing Patients' Sexual Concerns Sexuality constitutes an important indicator of health-related quality of life and overall health in cancer patients [50]. Cancer and medical/pharmaceutical therapy can have adverse effects on sexual health and sexuality, resulting in various unfavorable physical side effects and psychological difficulties [51]. Consistent evidence accentuates the significance of healthcare professionals in addressing sexual concerns and difficulties cancer patients encounter during treatment, in the follow-up, or the survivor phase [50, 52]. Sexual concerns and difficulties that cancer patients encounter include erectile dysfunction, lack of libido, dry ejaculation, climacturia (urine leaking during orgasm), anorgasmia (difficulty to reach orgasm), difficulty of enjoying sexual activity, pain during intercourse, body image concerns, and feeling sexually unattractive [50, 51]. Studies have demonstrated that sexual problems related to the medical treatment received due to cancer often are not discussed by healthcare professionals [53–56]. A recent study by Wazqar (2020) highlighted the importance of improving sexuality knowledge of healthcare professionals working in cancer care, by introducing continuing education programs on sexual health, and making resources, such as educational materials and clinical checklists available [50]. Beyond medical professionals, psychologists also may not receive supervised training on sexual health concerns and tend to rarely ask about sexual health [57]. Therefore, psychologists must seek relevant training and ensure that they assess and address sexual concerns of cancer patients.

Addressing Patients' Spiritual and Religious Beliefs and Needs The American Society of Clinical Oncology (ASCO) emphasizes the importance of all healthcare providers offering spiritual care within their standard practices for all cancer patients [58, 59]. Psychologists play

an important role in addressing patients' spiritual and religious beliefs and needs. Spirituality entails wide-ranging humanistic concerns and developmental facets of an individual's life that are grounded on personal values, as well as on personal, societal, and community needs [60], while religiosity alludes to the extent of participating or adhering to practices and beliefs regarding a religion shared by a specific community [61]. Severe diseases like cancer have an impact on the individual's mind, soul, and body, which inevitably elicits spiritual questions about values, relationships, and meaning [62]. Spiritual and religious beliefs serve as an important source of support, hope, and strength for a lot of cancer patients who are confronted with the ambiguity of the present and the unpredictability of the future [63]. Often patients feel the need to bring up spiritual concerns without expecting spiritual answers from healthcare professionals, and it is crucial that healthcare professionals do not reply to patients' spiritual concerns with dismissive or judgmental comments [62]. It is recommended that a spiritual assessment is conducted to assess for sources of support, hope and strength for the patient, any prayer practices, means of expressing spirituality, what meaning the patient ascribes to suffering and death, the patient's role in a religious neighborhood or district, and the form of religious or spiritual support the patient seeks [61, 63]. Clinicians must assess and discuss openly with patients about their religious and spiritual beliefs and needs [61]. Some examples of questions are as follows: "Are there any spiritual or religious resources upon which you can draw to help see you through this?" "If you're a religious person, how are things between you and God?" "How are things with your family and friends?" "Is there anyone with whom you need to 'make up'?" "Is there anyone to whom you need to say 'I love you' or 'I'm sorry'?" [61, p. 1387]. Healthcare professionals, as well as patients and their caregivers carry their personal values, experiences, beliefs, and biases regarding spirituality and religion to each clinical meeting/session and to the therapeutic relationship [62]. It is proposed that oncology professionals including psychologists exhibit their respect for patients' and caregivers' spiritual beliefs by showing that they are also engaged in spiritual aspects of living, as this can establish an ambiance of trust and reassurance enabling patients and their caregivers to reveal their spiritual and religious needs [62]. Psychologists can incorporate religious or spiritual coping strategies in the case formulation and treatment plan of cancer patients [63]. Individuals who struggle with spiritual concerns can also be referred to pastoral type care.

Providing Culturally Sensitive Healthcare Another unmet need is providing culturally sensitive healthcare. Multicultural competence is a skill that psychologists working with cancer patients and their caregivers need to acquire. That is, they need to be aware of the cultural, religious, and spiritual beliefs and traditions of the patient, as these exert an influence on the patients' and their caregivers' understanding of the disease, the way they experience it, their preferences about the care they receive, and the meaning and ways of coping with death, loss, and dying [62, 64, 65]. Cultural factors can affect the discussion of certain symptoms between patients and healthcare professionals [38]. For instance, women of a specific culture may feel uncomfortable to discuss gynecological complaints with a male healthcare professional [66]. Psychologists need to be culturally sensitive to these matters (i.e., when discussing symptoms with patients of culturally diverse backgrounds) and also inform and train other professionals in providing culturally sensitive services. It is important to listen to and respond to the concerns of the patients in a sensitive manner by asking patients what they feel comfortable of discussing or if they touch upon issues of concern to patients. It is vital to also ask patients what language they feel comfortable of using, to learn more about the values of people from different cultural or social backgrounds, and to respect and accept differences between cultures as well as within cultures (see also Chap. 13, this volume).

Addressing Physical and/or Psychological Difficulties Patients Refrain from Reporting Cancer patients may avoid reporting physical and/or psychological difficulties for various reasons, which constitutes an unmet need that can adversely impact their quality of life. It is important for psychologists to know that often patients tend to refrain from reporting pain symptoms or underestimate symptoms due to fear that aggravation of symptoms may be indicative of disease progression [38]. They may also refrain from reporting their symptoms because of fear that the oncologist will stop medical treatment, they have not received care for their common complaints, or they think that these symptoms constitute unavoidable consequences of cancer and medical therapy [38]. Especially, older patients tend to be hesitant when it comes to asking questions since they may regard asking questions as rude or that it is improper to make their own decisions about their health [67, 68]. Additionally, patients and significant others may express reluctance in discussing psychological difficulties due to unpleasant experiences within the healthcare system that led to a loss of trust in the system [38]. Thus, psychologists need to be aware of the aforementioned and attempt to establish a trusting therapeutic alliance from the first encounter.

19.2.2 Psychologists' Role in Cancer Crisis Intervention

Psychologists also play an important role in crisis intervention. Crisis intervention is a type of help that is offered when someone encounters a sudden, frightening, and unfavorable life event [40]. Cancer can constitute a crisis situation. Crisis situations when a psychologist is called for a rapid and urgent psychological support include the following: time of cancer diagnosis – including biopsy and waiting period of results; when intrusive and anxiety provoking medical treatment(s) like surgery, chemotherapy, or radiation is proposed by the doctor; and when there is cancer recurrence and persistent struggle with cancer, especially when it happens following an extended period of recovery and survivorship [69]. The aforementioned situations may also require interdisciplinary help from other professionals (i.e., nurse, social worker, physician). During crisis, present-focus brief interventions are needed, which include listening to the patients' story (without force; allowing patients to share whatever they feel like sharing), encouraging the expression of emotions, and validating them and their experiences while aiding the patient in better understanding the situation. This approach also includes discussing concerns or doubts, and problem-solving solutions where possible. Solutions may include obtaining physician consultation, meeting with a social worker, discussing the risks and benefits of the decision to start or stop medical therapy or which type of therapy to receive, and discussing values-based actions for the near future [40].

It is pertinent to emphasize that time is a crucial factor for the patients, their families, as well as the healthcare professionals, including the psychologist. A delay of a day after a crisis, may be beneficial in permitting reflection and coming to terms with the illness or medical treatment and gaining the patient's and the family's approval. Reacting fast after hearing about the cancer diagnosis or medical treatment may lead to detrimental outcomes, such as delays in medical therapy and missing the opportunity for prolonged survival or recovery [40]. Psychologists then can help balance this sense of urgency with a thorough decision-making and formulation of action plans. It is important for the patients' long-term quality of life to feel like they were the driver of their healthcare bus and that they chose the path forward.

19.2.3 Psychologists' Role in Training Other Healthcare Professionals Regarding the Delivery of Bad News

Psychologists by their training may be the appropriate professionals to help with the delivery of bad news and provide training to other healthcare professionals on this matter. Breaking bad news

is a common task in everyday clinical practice for physicians [70] and has a strong impact on the quality of life of patients, families, and health professionals [71]. Bad news denotes any information concerning an individual's health that can negatively and severely influence the person's view of his/her future [72, 73]. This entails prognostic information, like a diagnosis of malignancy [74], aggravation of the disease or failure of medical treatments to treat the cancer, and when the patient is dying or has died [75, 76]. Difficulties encountered regarding breaking bad news include insufficient time to address the emotional needs and reactions of patients and family members [77, 78], lack of agreement among healthcare professionals within the team [77, 79], and the content and timing of the conversation of disclosing difficult information and who it must be disclosed to [77, 80, 81].

Additionally, delivering undesired information to patients in an appropriate manner constitutes the foundation for their compliance with medical treatment [73], and is related to higher patient satisfaction and better adaption to cancer [82]. Patients who become aware of their physical health and the way it is progressing tend to be better prepared to make informed decisions, have a higher sense of mastery, and tend to be less likely to undergo unsuitable or ineffective therapies [83, 84].

Breaking bad news is challenging both for healthcare professionals who are disclosing unfavorable news as well as those receiving the bad news [85]. Even though breaking bad news is a task that doctors usually conduct, since it includes discussing the diagnosis about a medical condition and how it is progressing, other healthcare professionals also have an important role at various time points and situations [86]. That is, healthcare professionals, including psychologists prepare patients for receiving bad news, clarify the information provided to patients, help patients make informed decisions as well as adjust to the implications of such bad news [87]. The process of disclosing difficult news is often ongoing and entails numerous interactions with patients. Unfortunately, health professionals may be ill equipped or untrained in how to deliver bad news [70]. Psychologists can train other healthcare professionals. Some recommendations to be included in such a training are the following.

The ideal setting of delivering bad news is a quiet room, where doctors and patients can sit down, without any barriers between them (i.e., an office desk, books, medicines) and without interruptions and time restrictions [88]. Gao (2011) emphasizes the importance that doctors initiate this discussion in a warm and caring manner, by asking open-ended questions, such as "What have you been told about your health so far?" or "What is your understanding of the reasons you did the biopsy/ultrasound/MRI?" [73]. This will enable the doctor to obtain an understanding of the patient's perception of his/her medical situation. It is important to attend to non-verbal communication, including facial expressions, hand gestures, eye contact, body postures (i.e., open or closed body posture, leaning backward or forward), paralinguistic speech features, like pauses, rate and tone of speech, and behaviors during the conversation, like interruptions [89]. Prior to the delivery of bad news, it is vital to obtain the patient's consent regarding how much information about their health they wish to learn [88]. Then, it is important to provide a corresponding explanation of medical terms, using simple language or metaphors that can be easily comprehensible to the patient [90]. It is vital to avoid over-prognosticating since nobody has knowledge of the exact future of anybody and never use the phrase "At least you…" [91].

Responding with empathy to patients after the delivery of bad news is important [88]. When a patient remains silent, it may be helpful to allow some time for processing, make a reflective statement ("Words appear to be difficult today"), and then ask open-ended questions regarding their feelings and thoughts and allow some time for the patient to express his/her thoughts and feelings. It is important for doctors to be careful when using empathic statements to acknowledge their own sadness or other difficult emotions so that they do not shift the attention from the patient to themselves. Even when doctors discuss about their own feelings, they should maintain the focus on the patient and how the patient is feeling

and thinking after hearing the bad news. Doctors must be cautious not to make promises they cannot keep. It is crucial, however, to sustain some hope, even when the only hope the doctors can install is that for alleviating pain, mitigating the side effects of medical treatment, and reassuring patients and family members that they will be supported throughout the cancer journey [91]. Discussing with patients regarding the treatment plan, sharing decision-making, and allowing time for patients to ask questions are also essential [88]. Some training programs are incorporating delivery of bad news in their courses (e.g., "SPIKES" program) [88]. This program constitutes a standard framework on how to properly deliver unfavorable news to patients [91, 92] with good outcomes in health professionals' preparedness and readiness to deliver bad news [93].

19.2.4 Role of Psychologists in the Management of Dynamics Within the Interdisciplinary Team

An interdisciplinary team approach improves care for the patient and can provide support to the medical team when encountering challenging situations [94]. Psychologists, as part of the interdisciplinary team, cooperate with other healthcare providers to offer thorough and holistic care to patients, family, and significant others and also offer educational training and consultation to other professionals of the team [31, 95]. The role of the psychologist is to also provide support to other healthcare professionals within the oncology system [96]. This includes managing team dynamics, like interprofessional relationships, communication, and collaboration as well as team building and conflict management skills [97, 98]. Experiencing conflict is an inevitable and typical part of an interdisciplinary team, and psychologists can facilitate bringing conflict to the surface so that it can be addressed, discussed, and resolved [23]. Conflict may stem from various factors within the system, such as shortage of resources, stress related to the large number of cases, and inadequate organizational management [23]. Conflict may be aggravated with dysfunctional team dynamics, which entail poor communication, unclear team responsibilities and roles, and deficits in team leadership [99, 100]. When team communication is insufficient, patients' family dynamics may affect the dynamics of the interdisciplinary team, and vice versa, in a way that teams can involuntarily mirror or intensify conflict in the patients' family [101]. It is important for the psychologist to be aware and identify this parallel process in order to help team members build a repertoire of healthy communication and model functional dynamics for the patient's family.

19.2.5 Conducting Research and Contributing to Policy and Practice Guidelines

Psychologists trained in experimental and research methods are placed in an ideal position to determine research priorities within cancer care. Such priorities can entail assessing empirically based practices in the mental health sector and examining the comparative effectiveness of several forms of psychotherapy (i.e., individual, group, and family-based psychotherapy) offered to cancer patients and their caregivers [23] that focus on quality of life, functionality, and vitality in living. Also, conducting research facilitates the development of prevention programs to alleviate the risk of developing psychopathology and improve symptoms management (i.e., pain, fatigue) and quality of life in cancer patients. Other research areas that are important to examine include assessing the most ideal approaches to address advanced planning and illness management in palliative care with patients from various cultural backgrounds, gaining knowledge on the complex interaction among healthcare systems, healthcare professionals, patients, relatives, and significant others, and discovering the most suitable approaches of educating patients and their caregivers regarding palliative care [102]. Moreover, research should assess and identify the most suitable practices and approaches to maintain and ameliorate the men-

tal health of oncology healthcare providers as well as prevent the development of burnout and compassion fatigue [103]. Psychologists with expertise in various methodologies can utilize dynamic designs in their practice, such as idiographic approaches to assessment and treatment. Such idiographic methodologies are a way to empirically approach each person served and are dynamic wherein assessment and treatment are on a continuous loop where one feeds the other and changes are made based on the needs and circumstances of each individual. Adopting such an empirical mindset allows for the psychologist to be able to conduct research as they practice.

Psychologists can play a crucial role in the formulation of policy and practice guidelines for cancer patients. Historically, psychologists have not been present at national consensus groups relating to cancer care and palliative care, even to those on developing policies and making suggestions for psychological difficulties [23]. Psychologists' role in the scientific community is to also inform about and promote quality of life in cancer care through lectures, publications, and attending conferences. Therefore, we argue that an important role of psychologists is to disseminate results from research to other healthcare professionals, researchers, patient organizations and policy makers, both locally and internationally. Also, psychologists can advocate and promote their expertise so as to be included as integral members of policy development groups.

19.2.6 Knowledge and Expertise on Psychotherapeutic Approaches

Psychologists working in cancer care should also have the knowledge and expertise to employ evidence-based interventions and practices with strong research support that target quality of life, functionality, and vitality in living. Many times, interventions will need to be brief and targeted. Psychologists working in cancer care frequently sit with and validate patients' and caregivers' pain and suffering and focus on encouraging living in accordance to values even in the midst of suffering. Kasl-Godley and colleagues (2014) argue that sometimes the most important intervention is to observe and hold the suffering and pain of an individual, validate his/her feelings and experience, as well as the person's humanity, one that is full of failure, mistakes, doubts, kindness, resilience, and of important value to other people [23]. Additionally, it is important for psychologists to have knowledge and expertise in psychological treatments that effectively address psychological and physical challenges of living with a chronic life-threatening disease. A promising psychological intervention within the cancer domain that takes into account all the aforementioned is Acceptance and Commitment Therapy (ACT) [104], which we will discuss in more detail below.

In this section, we discussed the multifaceted roles of psychologists in cancer care. We will next discuss different forms of psychological interventions that have shown empirical support for use within oncology settings.

19.3 Psychological Interventions Applied in Cancer Care

Psychological interventions that have demonstrated support for use in cancer care stem from behavioral and cognitive-behavioral traditions. We will present these, with an emphasis on contemporary approaches (also called third-wave approaches), such as Mindfulness-Based Therapies and Acceptance and Commitment Therapy.

19.3.1 Cognitive Behavioral Therapy

Cognitive Behavioral Therapy (CBT) is a psychological intervention with demonstrated empirical support in alleviating distress and ameliorating the quality of life of cancer patients [105]. According to Beck (1993), psychological difficulties stem from inaccurate and distorted thinking patterns [106]. The aim of CBT is to identify the individual's cognitive distortions and irrational thinking which aggravates his/her abil-

ity to deal with stressful events in life and then challenge these distorted beliefs and Negative Automatic Thoughts (NATs), taking into account contradictory evidence from the environment. This process is purported to result in better mood and alleviation of psychological symptoms, such as anxiety, fear, and distress [107, 108].

CBT entails self-monitoring of thoughts, feelings, and behaviors, for example via the use of a diary, learning to examine the validity of thoughts and performing behavioral experiments to test them and practice the coping skills learned [109]. Cancer patients are provided with psychoeducation about how thoughts influence emotions and learn how to identify NATs and thinking errors, such as all or nothing thinking, selective attention, overgeneralization, negative predictions, and disqualifying the positive. Cognitive restructuring is utilized [110], in which patients learn to identify, assess, and modify faulty beliefs, cognitions, and evaluations regarded as responsible for their psychological distress [111–113]. With the occurrence of cancer, individuals' daily activities and typical routines are disrupted; thus, activity scheduling with the use of, for example, a diary sheet is employed in order to integrate back normal routines into their lives [110]. Patients are also taught to use the technique of distraction or "thought stopping," when encountering unpleasant and difficult thoughts [110]. Behavioral techniques are also employed and patients are encouraged to change their actions and routines, and these in turn will help them deal with the NATs and improve their quality of life [110]. CBT can be delivered through an individual or group format [114, 115].

A meta-analysis assessing the efficacy of CBT in 10 randomized clinical trials of 1939 breast cancer survivors and patients showed that at post-treatment, CBT had statistically medium-size effects on quality of life and large effect sizes for depression [116]. A recent meta-analysis, which incorporated data from eight studies to examine the effectiveness of CBT on depression, anxiety, and quality of life in early-stage breast cancer patients reported that patients who received CBT exhibited moderate ameliorations with regard to anxiety [117]. Nevertheless, no significant improvements in depression and quality of life were exhibited in patients receiving CBT within or after 4 months of therapy [117]. Another meta-analysis that included six studies showed that CBT did not significantly improve quality of life in breast cancer survivors (standardized mean difference = −0.016, 95% CI = −0.898 to 0.866, $p = 0.972$) [118].

Even though CBT is considered an empirically supported intervention for psychological disorders, most meta-analyses have failed to support its use to ameliorate quality of life in the long term within cancer care. However, there are limited studies that examine CBT across different settings and cancer diagnoses, with most studies examining the efficacy or effectiveness of CBT on the quality of life of females with breast cancer and with most studies not including long-term follow-ups. Thus, more research is needed, including other cancer types and more long-term follow-ups in order to be able to definitively recommend this kind of intervention more widely.

19.3.2 Mindfulness-Based Interventions

The most commonly utilized mindfulness approaches in cancer care currently are Mindfulness-Based Stress Reduction (MBSR) and Mindfulness-Based Cognitive Therapy (MBCT) [119]. Both MBSR and MBCT [120] interventions aim for self-regulation of the attention of present moment, as well as openness to and acceptance of the moment-to-moment experience [121]. MBSR was developed to assist individuals suffering from chronic health conditions, who did not show improvements in physical symptomatology with the standard medical care; with early work concentrating on chronic pain [122]. Rather than aiming to alleviate pain, MBSR aims to cultivate self-regulation through mindfulness. Based on this perspective, mindfulness is "paying attention in a particular way; on purpose, in the present moment, and non-judgmentally" [123, p. 4]. Suffering is alleviated as a result of holding a neutral, open awareness, permitting acceptance of thoughts and emotions

related to pain and pain sensations, without struggling with pain or ruminating about pain [123].

Mindfulness practices incorporated in MBSR entail formal meditation and informal practices, which encompasses becoming consciously aware while performing everyday activities [124]. Mindfulness meditation exercises such as "the body scan" encourages the individual to focus on the sensations experienced in a body part(s) and can be helpful for patients who experience bodily difficulties, such as females who underwent mastectomy or experience pain. Sitting meditation entails augmented awareness of the body, training the attention "muscle" by repeatedly returning to following the breath, and becoming increasingly aware of the thoughts that come to mind and learning that they are not their thoughts. Examples of informal mindfulness include mindful walking, mindful eating, mindful brushing of teeth, mindful bathing, and performing any daily task with conscious awareness [124].

MBCT, which combines CBT principles with those of MBSR, was developed to improve relapse prevention of depression [125, 126]. The MBCT mechanisms incorporate awareness and acceptance of the present moment so that patients learn to relate in a different way to their thoughts, feelings, and actions and disrupt key mechanisms that contribute to mood-related difficulties. MBCT varies from MBSR, as it focuses more explicitly on thoughts and the association between thoughts and mood [127]. MBCT is applicable for individuals facing stressful life situations like cancer, who tend to ruminate about the meaning and the causes of the disease, contributing to increased distress [127]. Even though MBSR and MBCT were developed as group interventions, the skills taught in these approaches can be applied in individual Mindfulness-Based Therapy with equivalent positive impact [124].

Findings regarding the empirical evidence of Mindfulness-Based Interventions on the quality of life of cancer patients appear to be promising. A randomized clinical trial of 229 females with stage 0 to III breast cancer following surgery, chemotherapy, and radiotherapy demonstrated superiority in MBSR ameliorated mood, breast- and endocrine-related quality of life, and well-being compared to standard care [128]. These findings persisted at the 3-month follow-up. Another RCT compared the efficacy of a group MBSR with a group supportive-expressive group therapy (SET) and a 1-day stress management control condition in 271 distressed female breast cancer survivors of stages I to III [129]. Results showed that MBSR was superior for alleviating symptoms of stress and ameliorating social support and overall quality of life in female breast cancer survivors at post-treatment [129]. Similarly, a meta-analysis examining the empirical support for MBSR and MBCT in female breast cancer patients demonstrated statistically significant short-term effects of MBSR and MBCT compared to usual care on health-related quality of life, sleep, fatigue, depression, and anxiety, with small effect sizes [130]. These small effect sizes were sustained and were statistically significant only for depression and anxiety up to 6 months after the interventions and only for anxiety up to 12 months after the interventions [130]. Consistently, a recent Cochrane systematic review that assessed the effect of MBSR on quality of life in the short term (at post-treatment), up to the 6-month follow-up, and in the long term (up to 24 months follow-up) in women with breast cancer demonstrated that MBSR showed small improvements in quality of life at post-treatment but really small or no differences at the 6-month and 2-year follow-up periods [131]. Collectively, these findings show that Mindfulness-Based Interventions are promising in improving the quality of life of women with breast cancer in the short term, yet do not demonstrate sustainability in the long run. However, these findings focus solely on breast cancer patients and have not been examined for other cancer types. Future research must include other oncology populations as well, in addition to more long-term follow-ups to reach more definite conclusions regarding the long-term effectiveness of Mindfulness-Based Interventions on cancer patients' quality of life.

It is important to note that MBSR and MBCT require patients to complete homework, which is quite extensive [e.g., 45 minutes of home-based mindfulness for six times per week; 122, 132].

Fashler, Weinrib, Azam, and Katz (2018) accentuate that this time commitment can be quite demanding for cancer patients who may find it difficult to complete homework in combination with the high burden of symptoms encountered and demands of cancer therapy [133]. Additionally, Fashler and colleagues (2018) emphasize that cognitive restructuring, which is incorporated in CBT, may not be appropriate for cancer patients whose cognitions about medical therapy, prognosis, and losses in valued life directions (i.e., interpersonal relationships, work environment) may not be distorted and may be realistic [133]. For instance, a cancer patient may have the thought "my family will be devastated when they hear about the diagnosis" or "I may die" [133]. This worry concerning whether aspects of CBT are consistent with the experiences of cancer patients has partly contributed in the growing interest in alternative approaches, such as acceptance-based interventions [119, 134], which will be discussed below.

19.3.3 Acceptance and Commitment Therapy

A third-wave CBT intervention that incorporates mindfulness and presents solutions to the drawbacks of the aforementioned approaches is Acceptance and Commitment Therapy (ACT) [104]. ACT is rooted in functional contextualism and purports a different mechanism of behavioral change, that of psychological flexibility in the face of difficult thoughts, emotions, and life circumstances [135]. Thus, the aim in ACT is a change in the relation with one's difficult emotions and thoughts instead of a modification of the content of what our minds produce [104].

Why ACT Might Be Helpful for Cancer Care?

There are several reasons that Acceptance and Commitment Therapy (ACT) constitutes a promising psychological approach in cancer care. Many researchers have emphasized that ACT can be particularly helpful in ameliorating the quality of life of individuals with long-term conditions, including cancer [136, 137]. ACT's aims appear to coincide with the difficulties encountered by cancer patients [136, 138]. Specifically, this approach accentuates that suffering constitutes a normal human experience [139]. Experiencing distress and a plethora of other emotions and thoughts as a result of a cancer diagnosis and medical therapy is a usual and expected response [138]. Additionally, living with cancer may elicit existential concerns in cancer patients, such as reflecting on mortality, on their identity as a person and their purpose as well as spirituality and religiosity at several phases of the cancer journey, including diagnosis, medical therapy and throughout the end of life [140–142]. Addressing patients' values (i.e., religiosity, spirituality, close interpersonal relationships) in the psychotherapeutic setting in cancer care is vital [63, 143]. ACT is a therapeutic approach that attends to what is meaningful to the individual – their personal values and goals in life [104]. It helps the individual discover meaning in their life and experiences which aids the person to achieve the best quality of life possible under the circumstances.

Contrary to symptom-reductive traditional CBT, which aims to change the frequency, form, and content of difficult thoughts, ACT aims to change the individual's relationship with his/her thoughts and thus reduce their behavioral impact [144]. The focus in ACT work in oncology is on validating the persons' experience (be it patients, caregivers, health professionals, etc.) and aiding the person to acknowledge scary thoughts and feelings as just normal internal experiences and to choose to live in the present in accordance with their values [145]. ACT helps individuals to recognize that they are not their disease or the things they are struggling with (a concept called self-as-context) and no matter what our minds produce or what we are going through, we always have a choice as to how we behave and act toward others and ourselves. Patients may not have a choice as to whether they will experience physical or psychological symptoms, but they do have a choice as to whether they choose valued-based actions that can improve their quality of life [145]. Although ACT does not directly aim for psychological symptom reduction, empirical evidence

has demonstrated that alleviation of such symptoms occurs as a result of actively engaging in valued life directions and enhancing acceptance of challenging internal experiences, such as difficult thoughts, emotions, and physical sensations [146, 147].

Theoretical Framework of ACT

ACT is based on behavioral psychology and is rooted in functional contextualism and Relational Frame Theory and aims to aid individuals in becoming psychologically flexible [104]. Psychological flexibility is conceptualized as "the ability to contact the present moment more fully as a conscious human being, and to change or persist in behavior when doing so serves valued ends" [148, p. 8]. Its inverse, psychological inflexibility, is considered as the primary cause of psychopathology and suffering [148]. Psychological flexibility is cultivated via six core processes or skills that are interrelated and together produce the Psychological Flexibility Model: acceptance (vs. experiential avoidance), cognitive defusion (vs. cognitive fusion), contact with the present moment (vs. dominance of the conceptualized past and future), self as context (vs. attachment to a conceptualized self), values clarification (vs. confusion about what is important for the person), and committed action (vs. inaction, impulsivity, or persistent avoidant behaving) [104]. These six interrelated skills are the mechanisms of change through which ACT exerts its impact [149].

ACT focuses on alleviating experiential avoidance, which is the person's unwillingness to stay in contact with particular private experiences (e.g., feelings, thoughts, memories, and bodily sensations) and his/her attempts to modify the form or frequency of these private events [150]. Experiential avoidance strategies can generate a short-term positive affect, such as feeling relieved from distress, yet will lead to the avoided event reappearing more strongly [151] as well as augmented distress and greater dysfunction [152]. Conversely, the willingness to make room for and experience difficult thoughts, emotions, and physical sensations in the service of one's values is considered as the "antidote to experiential avoidance" [152, p. 547]. Often cancer patients are encouraged to adopt a fighting spirit attitude (i.e., think positive and that everything will turn out to be just fine) which is impossible to achieve and entails avoidance of emotions, such as fear, anxiety, and hopelessness. In ACT, individuals recognize that it is normal and logical to feel whatever they are feeling and that fighting their feelings may create more suffering. They are thus directed at accepting their current situation, including their thoughts and feelings, and focusing on value-driven activities, small things or acts they can do at the moment.

Cognitive fusion is "the tendency for behavior to be overly regulated and influenced by cognition" [153, p. 84]. For example, a cancer patient who is obese may be fused with the thought that he/she has caused his/her cancer and ruminate concerning the unhealthy lifestyle choices he/she has made, which can lead to experiencing more psychological distress. With cognitive defusion techniques, the individual learns to observe thoughts from a distance so as to gradually understand that they are not facts, they do not rule behavior, and see them for what they are – just thoughts (words produced by our minds) and not literal truths [154].

Contact with the present moment diminishes as a result of experiential avoidance and cognitive fusion, since it is believed that being aware of the present moment brings up painful emotions and thoughts [148]. However, individuals often get lost in the past (e.g., how things used to be, how they were able to do things that they are not able to do now) or in the future (e.g., fearing that they may not be able to do things they wanted to do). When individuals live in the past or the future, they miss out any opportunity they have in the present to be able to do things that matter to them. By employing mindfulness training (similar to mindfulness practices discussed above), ACT promotes present moment awareness of both external events (utilizing the senses) and inner private events, such as emotions, body sensations, and thoughts [148]. The focus is on doing now what is of value to them, seeking vitality and importance in the now, however small or insignificant it may have seemed in the past. For

example, a person may focus on having meaningful conversations with his/her children now and talk about things that in the past may have been left unsaid or were waiting for the "perfect" moment to be able to say them. If for a patient it is important to visit the beach, they can do so now and not sit around waiting for the cancer to pass or treatments to end or until they feel better. Engaging in life now provides vitality and improves quality of living.

When an individual is stuck/ "fused" with attributes, such as "I am a cancer patient," the manner in which he/she views himself/herself becomes narrow ("self as content") [155]. That is, they may start to embrace the sick role and avoid doing things because of their condition. According to ACT, the self is "a context or arena for experience" (self-as-context) [155, p. 19]. Cancer patients are encouraged to develop a stable sense of self as observers (view the self as an arena of experiences), and not solely focus on the specific experience they have at that moment ("I am more than the disease") [155]. ACT encourages being consistently aware of present feelings, thoughts, and other private events (process) and notice that such private experiences are distinct from the experiencing self (context) [148]. For example, a cancer patient may have a decreased awareness of himself/herself as a whole and only see the self as his/her thoughts ("I am broken") and problems ("I am a cancer patient and nothing else"). These experiences restrict other facets of the self and may get in the way of "I am also a loving mother" or "I am a caring friend." By cultivating self-as-context, the individual recognizes that being a cancer patient is one aspect of their experience and does not define who they are. This gives them the power to be able to choose who they want to be and how they want to live even if they have cancer as an experience.

Values constitute long-term desired qualities of life [148], such as pursuing things that are meaningful for the individual (e.g., relationships, health, career, work) [152]. Cancer patients are helped to come to contact with their own values [63, 133]. When emphasis is placed on goals like feeling or looking good or being right, cancer patients may lose contact with what they find meaningful in life. They may act not based on what is meaningful for them, but in the service of what their minds are telling them [148]. When the patient lacks clarity of values, he/she loses contact with what he/she seeks in life [63, 148] and may fail to take essential steps that will provide meaning to their life now and empower them that they are able to still choose and do things of importance [152]. For example, a patient may avoid social interactions with friends or avoid experiences which can result in a romantic relationship, even though having close interpersonal relationships constitutes a very important value. In ACT, patients are encouraged to set short-term achievable goals/committed actions in line with personal values. Examples can include "I will walk for fifteen minutes per day, as I value being healthy" or "I will play one game with my child in the service of being a giving parent" [63, 145]. Thus, ACT focuses on cultivating commitment to pursue things in life that are in line with identified hopes and values, which leads to individuals experiencing vitality in the presence of cancer.

Another aspect that is targeted through ACT is self-compassion. Self-compassion consists of three key components: kindness (being understanding and warm toward oneself), a sense of common humanity (we are not alone in our suffering), and mindfulness (being mindful of moments of suffering or painful thoughts and emotions and view them as they are without avoiding them) [156]. These components are interrelated and interact to generate a self-compassionate mindset. Self-compassion is cultivated by promoting nonjudgmental observation of critical self-cognitions via strengthening self-acceptance and observer perspective taking [157, 158]. Self-compassion involves offering to the self the same level of love, understanding, care, and compassion that we would offer to someone else. Being self-compassionate allows the person to provide for themselves things that we may usually expect others to give us and feel disappointed when we do not receive them. It also empowers the person to recognize that they are doing the best they can under the circumstances and again instead of blaming or fighting with the self, the person can choose to do things that give

them meaning including self-care (e.g., getting a massage, painting one's nails, listening to favorite music).

An imperative role of the ACT approach is workability, which helps individuals understand whether their behaviors are working in relation to effectively reaching a resolution to a difficulty and progressing toward valued life areas [104]. For example, in the case of cancer, the therapist may nonjudgmentally ask the patient if excessively using painkillers or staying in bed (avoidance strategies) are working in the long term in reducing pain and examine the costs of employing these strategies in the long term on valued life directions. The identification of unworkable behavioral patterns that may offer short-term relief can help in facilitating behavioral modifications that are in line with long-term valued life areas [104]. ACT, as the word denotes, ultimately aims to mobilize the person to take action in their life however small that may be, as long as it is in the direction of their valued living path.

Empirical Research: Efficacy of ACT in Improving Quality of Life in Cancer Care

Empirical evidence provides promising findings for the use of ACT in cancer care. A methodologically robust RCT was conducted in 47 late-stage (Stage III or IV) ovarian cancer patients [159]. ACT was compared to Treatment as Usual (TAU), and patients received 12 individual sessions. Both conditions demonstrated ameliorated quality of life and mood at the end of treatment. Those receiving ACT demonstrated significantly higher improvements in depression, anxiety, distress, and quality of life compared to the TAU at post-treatment. Importantly, treatment outcomes were found to be mediated via ACTs' proposed mechanisms of action. Another study of 45 patients with mixed cancer severity and cancer type that incorporated 9 individual 45-minute ACT-based sessions [160] showed significant improvements in distress, mood, and quality of life at post-treatment. These positive effects were maintained at the 3-month follow-up. There were large effect sizes for mood and distress (>.80), and medium for quality of life (.50).

A small RCT compared ACT with Cognitive Therapy (CT) on changes in depression, anxiety, and quality of life in women with breast cancer [161]. Six women received ACT (focus on acceptance strategies) while six women were administered CT (focus on cognitive control strategies). Each intervention consisted of a total of eight sessions (3 individual and 5 group sessions). Findings demonstrated that the ACT showed greater and long-term effects (up to 12-month follow-up) compared to CT, with reductions in depression, anxiety, and enhancements in quality of life. Collectively, the findings discussed demonstrate ACT to be effective in improving the quality of life of cancer patients. These findings provide preliminary support for the use of ACT in cancer populations, particularly ovarian and breast cancer.

19.4 Self-Care, Self-Reflection, and Personal Development

Often psychologists report needing around 6 months to 1 year to adjust to working in cancer care [31]. Internal challenges that psychologists deal with include thoughts and doubts about their professional capacities of providing care, anxiety about their professional role and self-identity, and wondering about the meaning and value of life. Observing and responding to patients' suffering may elicit feelings of helplessness in psychologists in addition to lack of confidence in their ability to provide care and wondering if they can really provide help to patients and their caregivers [31].

Working with cancer, caring for patients' physical and psychological pain and suffering, constitutes one of the most meaningful and at the same time overwhelming experiences in a psychologist's professional life. Dealing with loss and death is an everyday challenge for healthcare professionals working in oncology settings. This kind of work carries a heavy emotional burden, and simultaneously has an existential impact upon the self which enriches psychologists' life, encouraging the professional to reprioritize

important values and act on them, leading to change and growth [96].

Offering services within cancer care must not be accomplished at the expense of psychologists' own quality of life [162]. According to Breen and colleagues (2013), healthcare professionals, including psychologists who work in high-suffering settings like cancer and palliative care, are susceptible to burnout, occupational stress, and secondary trauma [162]. Self-care practices for psychologists working in cancer care are particularly important in order to maintain their well-being and quality of life [96]. Psychologists can receive this training during their clinical practice [162]. Psychologists can cope with internal challenges when they are passionate about working in the cancer field, show willingness to become involved in this work and willingness to self-reflect, and know how to put boundaries relating to professional life and private life [31]. Also, the professional ability of psychologists working in oncology settings can be ameliorated through participation in a peer support group, having supervision and continuing self-education [31].

Although most clinicians recognize the importance of self-care, it is often hard to practice it [163]. Many clinicians may feel the need or believe that they are expected to act as a container for others' difficult emotions without becoming affected themselves [96]. Psychologists working in cancer care are also humans and are allowed to have feelings. Experiencing difficult feelings does not constitute an indication that psychologists are weak individuals or that they cannot perform their work. Often, there is the tendency to fight or control symptoms and internal states, and this struggle with thoughts, emotions, and physical sensations (i.e., pain) may result in suffering and dysfunction [135, 145]. It may be helpful to adopt an ACT-based stance to ourselves as we would with our patients and open up, make room, and acknowledge difficult thoughts, emotions, and physical sensations, instead of fighting them or trying to control them [104]. Although exerting control on emotions and thoughts is not effective and may lead to more suffering in the long term, healthcare professionals can control their behavior, that is their actions [104]. In the search for beneficial strategies, it could be useful for healthcare professionals to ask themselves what they would offer someone else if he/she was in their place, and then proceed to give that to themselves. This is being compassionate with oneself.

Self-compassion practices in healthcare professionals (similar to those offered for cancer patients) increase their ability to regulate emotions and may prevent fatigue and burnout [164], reduce stress, and ameliorate patient care and personnel well-being [165]. Healthcare professionals, including psychologists, may use self-compassion practices, such as kind self-talk with a warm and caring inner voice (i.e., "this is a moment of suffering") and kind self-touch [i.e., place their hand (physically or metaphorically)] on top of a painful feeling/sensation on their body and mentally send some care and warmth [166]. Other self-care practices include mindfulness exercises, grounding and connecting oneself to the body (i.e., slow deep breathing, stretching arms and neck, slowly pressing your fingertips together) [167], defusing from difficult thoughts and feelings, and investing in meaningful values-based activities.

19.5 Conclusion

Psychologists play a fundamental role in the assessment and the provision of psychological support for cancer patients and their families, in crisis intervention, in training other healthcare providers on breaking bad news, and in delivering effective psychotherapeutic approaches for this population that target quality of life. Their role also includes managing the dynamics in the interdisciplinary team and conducting research and contributing to policy and practice guidelines. Psychologists provide support to patients from the first signs of a problem to diagnosis, throughout medical therapy and recovery or the dying process, and to bereaved significant others following a patient's death.

Contemporary psychological interventions such as CBT and Third-Wave Cognitive Behavioral Therapies (particularly Mindfulness-Based Interventions and ACT) appear to be promising in improving the quality of life of cancer patients. The findings have shown that CBT and Mindfulness-Based Interventions are promising in improving the quality of life of women with breast cancer in the short term, yet do not demonstrate sustainability in the long term. Additionally, findings provide preliminary support for the use of ACT in cancer populations in ameliorating the quality of life of cancer patients both in the short term and in the long term. Future research must include various cancer populations as well and more long-term follow-ups to reach more definite conclusions concerning the long-term effectiveness of these approaches on cancer patients' quality of life.

Self-care practices for psychologists working in cancer care are pertinent in order to be able to effectively promote the quality of life of cancer patients, their family members, and significant others. Improvement in the care of patients suffering from serious diseases like cancer should include the entire person. It is of paramount importance that all healthcare professionals, including psychologists, social workers, physicians, nurses, and physiotherapists, remember that patients with cancer are not just patients, they are human beings.

19.6 Questions That Can Be Used for Learning/Testing

- What is the role of psychologists in cancer care? Discuss and elaborate.
- Which are the most common unmet needs of cancer patients? Discuss and elaborate.
- Which individuals are most vulnerable to encountering fear of cancer recurrence?
- Which are important components for healthcare professionals to take into consideration when breaking bad news?
- Which behaviorally based psychological approaches have shown effectiveness in improving the quality of life of cancer patients? Discuss.
- Why Acceptance and Commitment Therapy might be helpful for cancer care?
- Why self-care is vital for psychologists working in oncology settings? Which are some self-care practices recommended for psychologists?

19.7 A Topic for Discussion That Can Be Used in Teaching

- The roles of psychologists in cancer care
- What is a promising intervention for cancer care and what are its tenets?

19.8 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

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19.9 Research in Context

A recent important paper that takes into consideration the substantial burden of individuals with chronic diseases, such as cancer, on their quality of life is the manuscript by Karekla et al. (2019) that focuses on providing recommendations for digital interventions to ameliorate adherence and engagement in chronic illness sufferers [168]. An emerging need for providing home-based psychological services to this population exists due to difficulties, including mobility, access, waiting time, and transportation. Digital interventions may address this need by providing psychological services to improve their quality of life. It may be particularly useful to employ digital interventions in cancer care, even as an adjunct to face to face therapy. Karekla and colleagues (2019) provide 10 recommendations grouped within four dimensions for the implementation of best practices in developing digital interventions with the aim to engage and help chronic patients adhere and engage with the provided interventions [168]. These recommendations emphasize that the first step is a priori theoretical planning. This planning should involve considerations of adherence and engagement for the specific target problem (e.g., quality of life in cancer patients) utilizing a digital theory-driven approach such as persuasive technology and gamification theories. Interventions should also be based on theory-driven empirically supported psychological interventions for the specific problem to be addressed [such as Acceptance and Commitment Therapy which demonstrated strong empirical support for pain management; 169]. A priori

planning should also consider ethical issues that relate to the specific problem and the digitalization of assessment and interventions and how these will be addressed should they arise (e.g., how to deal with a suicidal client) [168]. Another recommendation is to incorporate principles of positive reinforcement through features that consist of rewards (i.e., budges, visual trophies), praise (i.e., words, sounds, images), suggestions (i.e., for promoting sleep hygiene), liking (i.e., aesthetically appealing system), similarity (i.e., observing somebody they regard similar to them behaving in a certain way) and social role (i.e., a virtual character presented as a co-traveler and a healthcare specialist). Human interaction, such as getting a permission to electronically interact (i.e., providing encouragement, tailored feedback) with patients, is also encouraged. Adherence to digital interventions may be improved by frequent updates of new content, including prompts that inform about updates. Another recommendation is that digital interventions be also tailored to the population's needs and user characteristics (i.e., gender, duration and severity of cancer, quality of relationship with partner, and perceived social support). Assessment of patients' computer literacy and subsequent provision of easy tutorials and technical assistance based on their needs may be beneficial, in addition to setting clear expectations and simple instructions. Finally, utilizing web-metrics to measure inactivity is suggested as this may be helpful in using prompts to motivate patients to reengage [168]. One program currently being developed based on these recommendations is the I-CAN-ACT project [(A Brief Intervention for female breast CANcer based on Acceptance and Commitment Therapy (I-CAN-ACT)]. This project aims to examine in a randomized clinical trial (RCT) the efficacy of a brief ACT-based intervention for both depression and physical pain (6 sessions) compared to a waitlist control on various outcomes, such as quality of life, physical pain, and psychological symptoms (depression, anxiety) in women with breast cancer [170].

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20 The Role of Patient-Reported Outcomes (PROs) in the Improvement of Healthcare Delivery and Service

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20.1 Introduction

The nature of healthcare is constantly evolving. Healthcare systems historically focused on the prevention and treatment of infectious diseases are increasingly engaged with the management of chronic long-term conditions such as heart disease and diabetes which are resource intensive [1].

There has also been a gradual shift from a biomedical model to a bio-psychosocial model of care [2–4]. The traditional biomedical model focused mainly on the biological basis (pathophysiology) of disease with the clinician as the major player in the provision of care, while the patient has little or no say [2, 5]. Conversely, the bio-psychosocial model considers the intricate relationships between biological, psychological, and social factors that influence health, disease, and healthcare delivery [5].

The bio-psychosocial model of healthcare underpins the concept of 'patient-centred approach' or 'person-centred care' which is a broad, emerging, and evolving healthcare concept that encompasses and focuses on the various principles of care, support, and treatment *that matter most to individual patients* [2]. The Institute of Medicine (IOM) acknowledged patient-centred care as one of the aims for healthcare systems and defined it as "*care that is respectful of and responsive to individual patient preferences, needs, and values….that ensures that patient values guide all clinical decisions*" [4].

Understanding and capturing the patient perspective is therefore vital for the delivery of high-quality patient-centred healthcare. The systematic collection of patient-reported outcomes (PROs) through the administration of appropriate patient-reported outcome measures (PROMs) and the utilisation of these data can be used to assess and drive improvements in quality of healthcare.

This chapter explores the role of PROs in the evaluation and improvement of healthcare services. Specifically, the chapter will enable readers to (a) understand the need to evaluate quality in healthcare and the potential role for PROs; (b) understand the benefits of using aggregate and patient-level PRO data in the improvement of healthcare in routine clinical practice; (c) appreciate the barriers that may be encountered when using PROs in routine clinical practice; (d) and appreciate the need for an integrated approach to healthcare.

20.2 Quality in Healthcare

Quality in healthcare may be defined as "an optimal balance between realised possibilities and reference normative frameworks" [6, 7]. Realised possibilities may include actual care provided, health, disabilities, mortality, patient experiences, or facilities, while reference normative frameworks may refer to professional standards, guidelines, patient expectations, societal ideals, and cultural values [6]. Healthcare quality may be assessed based on the extent desired health outcomes are fulfilled [8].

However, this is an abstract concept that is difficult to measure directly. For this reason, healthcare providers and researchers measure aspects of healthcare that may serve as indicators of quality [9]. These 'quality indicators' fall into three groups:

- Those pertaining to *structures* that reflect the availability of services or resources [10]
- Those relating to *processes* of healthcare and referring to the actual care delivered. [10]
- Those concerned with the *outcomes* of medical care which may be observed by the clinician or reported by the patient (PROs) [10]

Clinician-observed outcomes of healthcare, such as mortality and survival rates, have long been favoured as indicators of the quality of care [11]. While these clinical parameters are crucial in the management of patients, it has been recognised that relying on these alone may be insufficient [12]. Particularly when assessing the quality of care provided to patients with chronic medical conditions (e.g., chronic kidney disease), where patients may survive for a number of years while experiencing suboptimal health and quality of life or pre- and post-surgical intervention [13–15]. As patients are best placed to assess and provide feedback on the quality of care they receive and the quality of life they experience, the use of PROs could play an important complementary role to clinician-observed outcomes.

20.3 PROs and Quality Improvement of Healthcare

The collection and use of PROs is well established in research settings such as clinical trials and observational studies to evaluate the effectiveness, cost-effectiveness, and tolerability of interventions from a patient perspective [16]. Their implementation for the improvement of healthcare delivery and services has been less widespread.

However, in recent years, interest in the routine use of PROs to enhance the quality of patient care has increased. Aggregate PRO data may be used to assess, and compare, the performance of hospitals or healthcare providers, while health authorities may use such data to inform their decisions on commissioning and payment of healthcare services. On the other hand, clinicians may be more interested in patient-level PRO data for the clinical management of individual patients in routine practice.

Lord Darzi stated in his 2008 report that *"High quality care should be as safe and effective as possible, with patients treated with compassion, dignity and respect. As well as clinical quality and safety, quality means care that is personal to each individual"* [3]. The implication of this statement is that the delivery of high-quality care, which is person-centred, may be achieved when patient experience, their safety, and the clinical effectiveness of treatment are continually evaluated and improved upon. This may be accomplished by using a variety of measures including those that capture patient perspectives such as patient-reported outcome measures (PROMs) and patient-reported experience measures (PREMs). Figure 20.1 shows the interrelationships between elements of high-quality care, PROMs and PREMs.

Following the publication of the Darzi report, the National PROMs programme was implemented in 2009 for certain elective surgeries in England to evaluate and benchmark the performance of healthcare providers. Conversely, healthcare providers countries such as Denmark, Sweden and the USA have focused on the use of PROs for individual patient care [17].

20.4 The Role of Patient-Level PRO Data

There is growing interest among clinicians, patients and healthcare providers in the use of PROs for the clinical management of individual patients in routine practice [18, 19]. This may be due to the drive to foster person-centred care and an increasing recognition that traditional clinician-reported outcomes and clinical parameters may not adequately capture patients' health-related quality of life (HRQOL) and may underestimate symptom burden [20, 21]. PROs, which capture the patient perspective of their health status, may complement traditional measures of health status when collected and used appropriately.

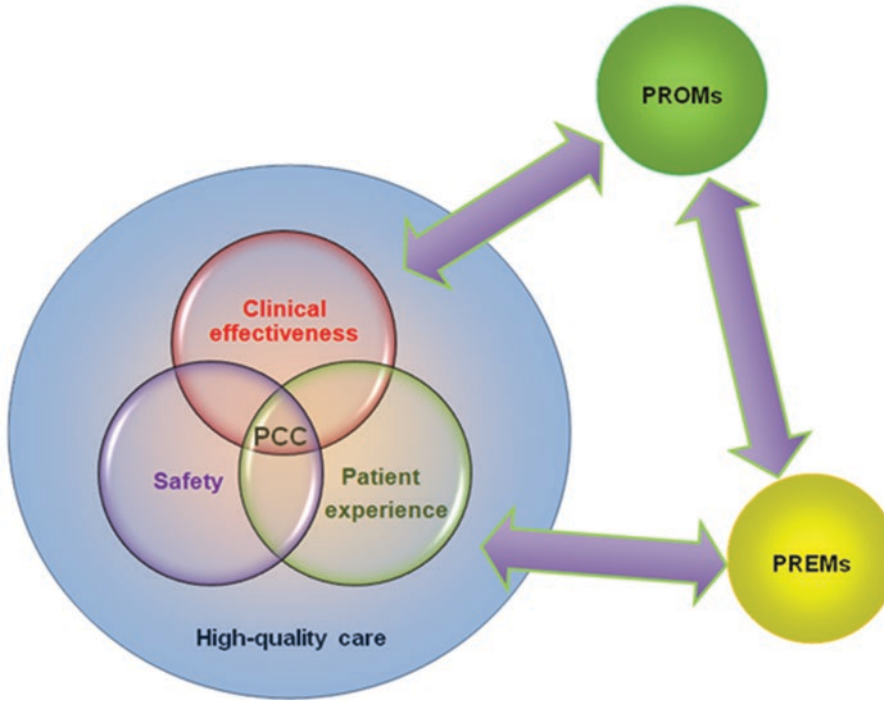

Fig. 20.1 Interrelationships between PROMs, PREMs, elements of high-quality care, and PCC. PCC, patient-centred care; PREMs, patient-reported experience measures; PROMs, patient-reported outcome measures [22]. (Used with permission from: Olalekan L. Aiyegbusi, Derek Kyte, Paul Cockwell, et al., A patient-centred approach to measuring quality in kidney care: patient-reported outcome measures and patient-reported experience measures, *Current Opinion in Nephrology and Hypertension*, 26(6), p. 442–449, 2017. https://doi.org/10.1097/MNH.0000000000000357)

20.4.1 Potential Impact on the Processes of Care

Early research into the use of PROs in routine clinical practice found evidence of its potential impact on processes of care particularly patient-clinician communication [23–26]. Research has shown that the appropriate use of PRO data may facilitate patient-clinician communication [27] by ensuring that aspects of health that matter to patients are highlighted for discussion during clinical consultations.

Patients and clinicians may value treatment outcomes differently and so have conflicting priorities in terms of treatment goals especially for long-term conditions where full recovery is not a likely outcome and patients are managed for long periods. For instance, a patient with advanced chronic kidney disease may consider the ability to carry out their daily activities as the most important outcome and prefer their treatment focuses on improving their physical functioning, while the clinical team might place greater emphasis on controlling creatinine levels or improving survival. [19]

While some might argue that the clerking of patients during clinical consultations is sufficient to generate all the required information about a patient's health, issues such as time pressures during clinics and the reluctance on the part of many patients initiate these discussions, meaning that this may not always be the case [19, 27].

Routine clinical practice often demands that difficult treatment decisions are made after issues such as the trade-off between potential therapeutic benefits and side effects have been considered. In addition to enhancing patient-clinician communication, the use of PROs could foster patient engagement in these discussions and promote shared decision-making [27, 28]. This may not only empower patients but also increase their satisfaction with care and adherence to treatment [27].

Experience at Partners HealthCare, a large multihospital system in Boston, Massachusetts, USA, has shown that as comfort with the use of PROs in

clinical care has grown, feedback has increasingly underscored that clinicians find collecting PROs to be 'beneficial rather than burdensome'. Evidence from experienced users suggests that PRO collection is not only feasible and good for clinical care, facilitating early identification of problems and promoting shared decision-making, but also may enhance physician satisfaction and prevent burnout through improvements in workflow [29].

20.4.2 Potential Impact on the Outcomes of Care

20.4.2.1 Influence of Technological Advances

Technological advances within the last two decades have sparked interest in the development of electronic PRO measures (ePROMs) (see also Chap. 8, this volume). This transition from traditional paper-based collection of PROs to ePROMs has been facilitated by the rapid adoption and increase in ownership of electronic devices such as touch screen smartphones and tablet computers [30]. For instance, in 2017, about 77% of American adults reported owning a smartphone compared to 35% in 2011 [31]. There are numerous advantages of collecting ePROMs that have also contributed to this progression (Box 20.1).

Box 20.1 Advantages of Collecting ePROMs

Patient-related:

- Lower incidence of missing data
- Increased acceptance rates (facilitated by the growing ownership of electronic devices)
- Computer-adaptive testing could assist with tailoring of questionnaires to individual patients

Healthcare provider-related:

- Lower administrative burden
- Elimination of secondary data entry errors associated with paper questionnaires

Various studies have established the measurement equivalence of ePROMs to paper questionnaires thus providing the assurance that electronic versions of existing paper-based questionnaires have similar measurement properties [32–34]. Other studies have focused on the acceptability and feasibility of using ePROMs in routine clinical practice at individual patient level. The majority of these studies have reported high acceptance rates among patients and a general preference for ePROMs over paper-based PROMs. [35–39] In addition, they have also demonstrated that it is theoretically feasible to use ePROMs in clinical consultations, albeit with numerous challenges to overcome including appropriate health informatics infrastructure, selection of appropriate measures and alert thresholds, training and support for staff and patients, and overcoming embedded work practices [18, 28, 40–42].

20.4.2.2 Benefits of ePROMs for Individual Patient Care

ePROMs may be completed by patients in clinic, with or without clinical supervision, or remotely in an unsupervised setting (such as subject's home, workplace). Each of these settings has its advantages as well as disadvantages (Table 20.1).

Remote completion of ePROMs between clinic appointments allows monitoring over time of patients' symptoms and experiences of disease and treatment. These data may enable clinical teams detect functional and psychological problems earlier. This information could assist patients and their clinicians in making informed treatment decisions and potentially support the tailoring of care to individual patient needs. These ePROM systems could be programmed with algorithms that analyse patient responses in real time and automatically send alerts to clinical teams when preset thresholds are exceeded. Such alerting capability may facilitate prompt clinical intervention and allow rapid referral to appropriate specialist care when necessary. Evidence from recent RCTs of ePROM systems in oncology suggests that the use of ePROMs enhances symptom management and individualised care in routine clinical practice [43–45],

Table 20.1 Advantages and disadvantages of PRO completion in clinic and remote settings

Setting	Advantages	Disadvantages
Clinic	Risk of patients forgetting to complete PROMs is eliminated Patients who are unable to self-complete may receive assistance from members of the clinical team	Patients may feel hurried and there may be limited privacy in a busy clinic If completed in the presence of clinicians, patients may be reluctant to provide their true perspectives
Remote	Patients may find it easier to use their own devices Patients can decide when to complete questionnaires without interference The risk of infection from using shared devices is eliminated	Patients may forget to complete questionnaires Paper questionnaires would require posting which would take time

improves patient survival [46, 47], and encourages treatment adherence and is cost-effective [48–50].

An example of an ePROM system that is currently being used in the clinical management of patients is AmbuFlex [51]. This generic telehealth system was developed in Denmark for the collection of PRO data to support symptom assessment and clinical decision-making in outpatient settings [52]. The ePROM data assists clinicians in deciding whether there is a need to schedule outpatient appointments for several chronic conditions, including asthma, chronic obstructive pulmonary disease, epilepsy, sleep apnoea, and cancer. This has reduced the need for unnecessary outpatient appointments, thereby encouraging efficient utilisation of healthcare resources [51, 52].

20.5 The Role of Aggregate-Level PRO Data

PRO data may be used at aggregate level to improve the delivery of healthcare services by informing patient choices, audit and benchmarking of hospital performance, determining value-for-money and informing value-based healthcare provisions and reimbursement decisions, and complementing data captured by disease registries.

20.5.1 Inform Patient Choices

Patients are not only the source of PRO data, they may also be potential users of the information they generate [53]. Patients considering a particular treatment could gain valuable insights on variations in patient outcomes at hospital and/or clinician level from the comparison of aggregate PRO data provided by previously treated patients [53]. Such information could help patients make informed decisions about where and who they choose to provide their treatment. However, in practice many other factors (including distance from home) also influence patients' preference [16]. Aggregate PRO data could also improve patients' understanding of the potential benefits they may gain from treatment. NHS choices publishes provider-level outlier data for PROM eligible procedures as part of a 'score card' [16]. However, at present, there is limited evidence that PRO data is actively used in this manner [14]. For such data to meaningfully inform patient care, first requires selection of PROMs that capture outcomes that matter to patients and systems to capture such data that have been co-designed with patients to promote inclusivity and uptake and minimise missing data. Once data is captured and analysed, user-friendly, accessible patient information should be provided and signposted to those accessing the healthcare service [14, 16].

20.5.2 Audit and Benchmarking of Performance

PRO data can facilitate the audit and benchmarking of the performance of healthcare providers and provide evidence to support the need for improvements in healthcare delivery and service. Variations in PRO data, between hospitals and between clinicians, will naturally generate questions about possible explanations, the quality of healthcare services provided and the expertise of clinicians. High performing centres can be used as case studies for good practice learning. The PRO data could facilitate dialogue between managers and clinicians, and guide the development of appropriate strategies to improve quality and efficiency [53].

Two main factors that may influence a hospital's average score are:

(i) The socio-demographic characteristics, including age, gender, ethnicity, and social deprivation of patient population treated at individual hospitals (including) which may influence the incidence or outcomes of particular conditions.
(ii) The nature and characteristics of hospitals, which may include the type and quality of facilities available and the expertise of clinicians.

Since 2009, the National Health Service (NHS) England has used PROMs to assess the quality of care delivered by NHS providers and quantify post-operative health gains from the patient perspective for initially four surgical procedures – hernia repair, hip and knee replacement, and varicose veins [53, 54]. However, following the NHS England Consultation on PROMs, the collection of PRO data on hernia repair and varicose veins surgery ceased in 2017 [54].

Currently, patients undergoing elective inpatient hip and knee replacements are invited to report on their condition-specific health pre- and post-operation, on a voluntary basis, by completing the Oxford Hip Score and the Oxford Knee Score, respectively [55]. The EuroQol EQ-5D is also completed by the two groups of patients as a measure of general health status, which may be useful for health economic assessments. The data is predominantly collected using paper questionnaires and case-mix adjusted for patient characteristics, which are beyond the control of hospitals. Anonymised data is available on the NHS Digital website [55].

20.5.3 Value-Based Healthcare Provision and Reimbursement Decisions

Value-based healthcare, defined as "*…the equitable, sustainable and transparent use of the available resources to achieve better outcomes and experiences for every person"* [56], is gaining traction globally. The main drivers of this shift from volume-driven fee-for-service practice towards value-based healthcare, where providers are paid based on patient health outcomes, include significant changes in population health, due to the rise in non-communicable diseases, pressure to improve the quality of patient care, and the soaring cost of healthcare [57, 58].

Although the use of PROs for value-based reimbursement decisions is presently limited, there is growing interest within value-based care initiatives to use PROs to provide patients with better information about treatment options including information on the outcomes of care they consider as priority [59]. There is also the potential that PRO data could ensure that healthcare delivery is prudent, providing the right care at the right time, with equitable, transparent, and sustainable use of resources [56, 60].

NHS Wales is implementing PROs at scale to deliver value-based healthcare to identify unmet need, unwarranted variations in practice, and identify potential service improvements, which would contribute to efficiency savings and the judicious and timely allocation of resources [61, 62].

Efforts to design reimbursement models that align better with the goals of patients, clinicians, and payers are ongoing. PROs could play a key role in value-based reimbursement decisions by

payers such as the Centers for Medicare & Medicaid Services (CMS) in the United States [12] or Clinical Commissioning Groups (CCGs) in England who commission healthcare services for patients.

Specifically, the use of PROs in this context may:

(i) enhance patient engagement in healthcare decision-making,
(ii) drive the improvement of healthcare services and delivery with a focus on patient-valued outcomes and not volume,
(iii) ensure that payers only pay for outcomes that actually matter to patients whilst keeping costs under control,
(iv) facilitate the procurement of the best healthcare services for patients.

Majority of existing PROMs were originally designed for research purposes and not for measuring provider performance and may lack the required level of sensitivity to compare treatments or provider performance, especially for low-volume conditions or procedures [58]. Consequently, there is a need for alignment between PROMs and measurement objectives and standardisation across settings to ensure that appropriate decisions are made based on the PRO data collected. The clarification of measurement objectives in value-based care may ensure that the outcome is improvement in the quality of care, from the patient perspective, and not just the determination of provider reimbursements [58]. If the primary goal is to determine provider reimbursement, then appropriate PRO performance measures (PROPMs) should be developed to assess provider performance and the results should be actionable in a transparent manner to providers [58].

20.5.4 Data Capture by Disease Registries

National or regional disease registries collect PRO data alongside clinical parameters of health status to facilitate improvement in healthcare by highlighting healthcare performance on outcomes valued by patients. For example, a recent review found that PRO data is being collected/piloted by 18 orthopaedic arthroplasty registries globally. These include the Swedish Hip Arthroplasty Register and the UK's National Joint Registry, which started collecting PROs in 2002 and 2009, respectively [63].

20.6 Potential Barriers

There are several practical, methodological, and attitudinal barriers to the use of PROMs to improve healthcare services and delivery.

20.6.1 Practical Barriers

The development and implementation of ePRO systems often require the investment of a considerable amount of financial, human, and information technology (IT) resources. Due to these upfront resource requirements, questions are often raised about cost-effectiveness, which could significantly influence the decision by healthcare providers to commission the development and implementation of ePROM systems. For policymakers, the cost and cost-effectiveness of ePROM interventions in comparison to existing follow-up care may determine whether crucial governmental and/or institutional support in terms of legislation or finance is secured [50].

Previously, logistical challenges in collecting, storing, analysing, and reporting PROs have been a barrier to their use in practice. However, recent technological advances and innovations have made these less challenging [64].

Practical barriers downstream when the purpose of implementation is to facilitate individualised care include time constraints during clinical consultations to review ePRO data with patients and inadequate clinician knowledge of PROs and how to address issues raised. [27]

20.6.2 Methodological Barriers

Methodological barriers to the use of PROs relate to the nature and design of PROMs/ePROMs themselves, in particular their psychometric properties. As mentioned earlier, most legacy measures were designed for research purposes and may not possess the level of sensitivity or reliability required for use in individual patient care or value-based assessments for reimbursement [58, 64]. There is a need to establish other measurement properties such as responsiveness to change and the minimal clinically important change to ensure that the PRO data collected is useful. [28, 65] Furthermore, PROMs, developed using traditional psychometric methods such as classical test theory, are more suited for group-level comparisons. Most legacy PROMs have only undergone traditional validation and may require further assessment using modern psychometric methods such as Item Response Theory and Rasch analysis before they may be considered ready for clinical use at the individual patient level. [66] Failure to ensure that the PROMs used are appropriate and valid may lead to significant post-implementation attrition rates.

20.6.3 Attitudinal Barriers

The attitudinal barriers centre around clinicians' opinions of the relevance and value of using PROMs, which are non-clinical tools, to capture patients' accounts of their health status, experience of treatment, and psychosocial information in their care of patients. A number of recent studies have explored in-depth the practice tensions, scepticism and divergent views among healthcare professionals (HCPs) regarding the use of PROMs and ePROMs in clinical care [19, 67–69]. Concerns about workload; individual values, beliefs and priorities; lack of specific competence dealing with issues relating to emotional problems; and interpretation of PRO data were noted as some of the determinants of HCP attitudes [19, 67–69]. As noted in the case study above, however, as clinical teams become more familiar with PROs they may find them more beneficial than burdensome [12].

An awareness of the tensions and challenges experienced by HCPs with PROs and their engagement and involvement in ePROM system development, implementation, and integration are essential to overcome these barriers [19, 67–71]. Clear guidelines or actionable plans are essential to enable clinicians respond confidently and effectively to PRO data [72–75].

20.7 Other Issues for Consideration

When using PROMs for the improvement of healthcare, it is crucial that a number of issues are considered carefully as these could determine the success of implementation efforts.

First, different metrics can be derived from aggregate PRO data (e.g., the mean PROM score, subscale score, or the proportion of patients achieving a certain degree of improvement), and these may judge providers' performances differently or may be misinterpreted. [17] In addition, there is a need to carefully decide on and define what constitutes unacceptable performance. The relative risk of missing an underperforming provider must be balanced against unfair assessment [17].

The use of incentives to encourage the collection of PRO data also needs careful consideration. For instance, in England, the Patient Health Questionnaire (PHQ)-9, Hospital Anxiety and Depression Scale (HADS), and Beck Depression Inventory-II were once used as indicators for the Quality and Outcomes Framework (QOF) to assess the severity of depression, support clinical decision-making, and assess provider performance in general practices (primary care). General practices were rewarded based on the PRO scores. However, these PROMs were dropped in 2013 due to criticisms of over-diagnosis using the tools and the potential for gaming and manipulating the system through the exploitation of loopholes [16, 76, 77].

20.8 Integrated Approach to PROMs

As the number of PROMs and potential uses increase, we need to consider integrative approaches to PROM assessment to reduce inefficiencies in data acquisition and minimise patient burden. Multiple stakeholders, with differing needs, should work together to develop a non-burdensome pathway for patients to provide meaningful PROM data that may be used to support shared decision-making as well as provide a patient-centred data pipeline for audit, benchmarking, research, and real-world evidence generation. Careful consideration should be given to the rationale for PRO assessment and the harmonised approach to the selection, collection, analysis, and reporting of PROMs, integration into the electronic health record, and guidance on the optimal presentation and use of data [16, 78]. Further details on the steps to achieve this have been provided by Calvert et al. and LeRouge et al. [16, 78]

20.9 Conclusion

There is increasing evidence that the use of PROs could play a key role in improvement of healthcare at individual patient as well as population level. Priority should be given to research to explore the best ways to address the potential barriers and maximise the impact of patient-level PRO data for use in individual patient management and aggregate-level data to inform patient choices, audit and benchmarking of provider performance, value-based reimbursement decisions, and data capture by registries.

20.10 Questions That Can Be Used for Learning/Testing

1. What is 'patient-centred care'?
2. How would you define 'quality' in healthcare?
3. Are PROs used in your national or local healthcare setting? If so, how?
4. Which barriers to the use of PROs in routine clinical practice do you think are most challenging to overcome in your local context and why?

20.11 A Topic for Discussion That Can Be Used for Teaching

The need for an integrated approach to healthcare and the incorporation of PROs.

20.12 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

- Hjollund NH, et al. Use of patient-reported outcome (PRO) measures at group and patient levels: experiences from the generic integrated pro system, WestChronic. Interact J Med Res. 2014;3(1):e5.
- Calvert M, et al. Maximising the impact of patient reported outcome assessment for patients and society. BMJ. 2019;364:k5267.
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20.13 Research in Context

AmbuFlex System

AmbuFlex is a generic clinical telePRO system developed in Denmark for PRO data collection for use in clinical practice. The overall goal is to use PRO across nine diagnostic groups for clinical decision support to improve quality of care, promote patient-centred care, optimise the use of resources in the healthcare system, and for research purposes [52]. The diagnostic groups include epilepsy, narcolepsy, sleep apnoea, prostate cancer, colorectal cancer,

rheumatoid arthritis, renal failure, chronic obstructive pulmonary disease, and asthma. The specific aims for each patient group reflect the unique needs of the patients [51].

The system supports dynamic mixed-mode data collection (web-based and paper) and automatically prompts patients by postal letter or e-mail to answer the questionnaire online or in paper form at a scheduled time [52].

As at 2015, a total of 13,135 outpatients from 15 clinics were individually referred for remote ePROM follow-up and up to 18,912 questionnaires were collected. AmbuFlex is designed to make automated decisions based on the analyses of PRO data by an algorithm with pre-determined thresholds. Patients are divided into two categories: those who require clinical attention and so need an outpatient appointment and those who do not.

Schougaard et al. reported high completion rates of over 90% during follow-up and attributed this to the use of its mixed-mode data collection method. The average proportion of web-based answers at that was 56.7% [52]. A recent publication reflecting on the 15-year use of the AmbuFlex system noted that although a mixed-mode method of collection of PROM data was initially implemented to maximise response rates (66.5% of responses were paper-based in 2005), there has been a gradual preference for an electronic option (only 4.3% were paper-based in 2019) [79].

It was reported that the use of the AmbuFlex system led to decreases of 48% and 57% in hospital follow-up visits in patients with epilepsy and sleep apnoea, respectively [52].

Feedback from the patients and clinicians from the epilepsy outpatient clinic was positive. Patients reported benefits such as greater flexibility in care, saving of time, better communication with clinicians, and increased knowledge about their own disease [52].

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Introduction to Quality of Life in Drug Development

21

Bellinda L. King-Kallimanis, Lee Jones, and Lynn Howie

Contents

21.1 Introduction

In developing anti-cancer therapies, the gold standard question clinical trials have historically sought to answer is: *what is the impact of the experimental therapy on patients' overall survival?* However, as sponsors have looked toward bringing new therapies to patients more quickly, this has translated into more frequent use of sur-

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rogate endpoints as the primary clinical trial endpoint. A surrogate endpoint is defined as "an endpoint that is used in clinical trials as a substitute for a direct measure for how a patient feels, functions or survives" [1]. In other words, surrogate endpoints should reliably predict clinically meaningful effects. One of the most frequently used surrogate endpoints in oncology is progression-free survival (PFS). The concern with the use of PFS is that the relationship between PFS and overall survival, the clinical endpoint PFS is a surrogate for, is variable [2]. While overall survival is straightforward to capture, interpretation of the results can be complicated by crossover trial design, and in cancers with long natural histories, trials are expensive and can take decades to complete. This has led to increasingly stronger calls by oncologists and patient advocates to better understand *"feels and functions"* via patients' self-reported quality of life (QoL) to better assess the impact and clinical benefit of the therapy for patients and potentially identify issues with therapy toxicities [3].

Both the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) have provided guidance to industry on incorporating the patient voice in clinical trials. In 2006, the FDA published a draft guidance to industry on the use of patient-reported outcomes (PRO) in clinical trials; after public comment, this document became a final guidance in 2009 [4], and while a series of new guidances are under development [5], the 2009 guidance, at the time of writing, remains the reference document to industry for the FDA. It is important to note that the FDA guidance documents are not regulations and are therefore nonbinding recommendations; however, these documents do describe the current thinking at the FDA on that particular topic. They also provide a road map to help drug developers navigate a particular topic to ultimately gain licensure for their products. Around the same time as the FDA draft PRO guidance was published, the EMA published a reflection paper on the regulatory guidelines for use of health-related quality of life (HRQL) measures in the evaluation of medical products [6]. Subsequently, the EMA published an appendix to the Guidelines on the Evaluation of Anti-Cancer Medicinal Products in Man to address the use of PROs specifically in cancer clinical trials in 2013 [7]. The FDA 2009 PRO guidance focuses primarily on assessing the measurement properties of PRO instruments. Sponsors can use this guidance to develop their PRO strategy and provide appropriate evidence to regulators that the instrument(s) included in their clinical trial is reliable, valid, and sensitive to change over time for the target population. The EMA guideline appendix for anti-cancer medicinal products, on the other hand, focuses on endpoints and considerations related to PROs. For example, the guideline cautions "careful thought must go into designing and implementing PRO measures in the oncology clinical trial setting in order to investigate a well-formulated predefined hypothesis" and notes that there is no standard approach. Despite the different focuses, this EMA advice is, for example, in line with the FDA's frequent comment to come and discuss PRO endpoints with the Agency early.

In the regulatory context, the broad umbrella term of PROs is used to describe "a measurement that comes directly from the patient about the status of their health condition without amendment or interpretation of the response by a clinician or anyone else" [1]. While PROs and the concepts of QoL and HRQL are terms that are sometimes used interchangeably, the terms describe different concepts from a regulatory perspective. Broadly speaking, both HRQL and QoL are multidimensional concepts that aim to capture a person's assessment of their well-being, though HRQL dimensions are focused on a person's QoL using a health lens. In the EMA 2005 reflection paper, HRQL, within the drug development paradigm, is defined as "patient's subjective perception of the impact of his disease and its treatment(s) on his daily life, physical, psychological and social functioning and well-being" [6]. The FDA defines HRQL as "a multidomain concept that represents the patient's general perception of the effect of illness and treatment on physical, psychological, and social aspects of life" [4]. Using an example, a patient who reports how bad their pain is on a 0–10 numerical rating scale is providing a response on a PRO measure.

If pain severity on this 11-point numerical rating scale is the only PRO assessed in the clinical trial, this would be insufficient to understand patients' HRQL because multiple domains related to HRQL must be measured in order to report on how a treatment might have influenced patients' HRQL.

Regulatory advice from the FDA, EMA, and groups such as SPIRIT-PRO [8], the PROTEUS consortium [9], and SISAQOL [10] have provided recommendations and clear guidance that PROs should be treated similarly to other outcomes of interest in clinical trials. In this chapter, we aim to bring these resources all together to describe how PRO and HRQL data can be used to inform regulatory assessment of new therapies. This will include the considerations that go into clearly defined endpoints that could be used to assess efficacy or safety and ultimately end up in the product label. We will describe how the use and applicability of these data may vary with respect to disease setting. We will review commonly drawn conclusions with respect to HRQL-related endpoints in cancer clinical trials literature and discuss why some of these conclusions are problematic. We provide both a patient and a clinician perspective and discuss how real-word data might help fill a gap of efficacy and effectiveness, as well as safety.

This chapter will enable the reader to (a) identify key guidance and guideline documents for use of PRO data in cancer clinical trials; (b) know what are key concepts of interest in drug development; (c) recognize differences in how PRO data are used by different regulatory agencies; (d) understand how missing PRO data can influence the interpretation of PRO results from cancer clinical trials; and (e) hear both a patient and a clinician perspective in relation to PRO measures and the use of the data captured.

21.2 PRO Measures in Drug Labeling

Historically, the FDA and EMA have used different criteria to determine what patient-reported data will be included in their drug label. As there are multiple factors that can affect a person's conception of HQRL, the FDA asks that sponsors focus on concepts that are proximal to the drug effects, specifically of the drugs' ability to control disease as well as the adverse effects. For the FDA Oncology Center of Excellence (OCE), the concepts that are considered most proximal to the drug effect and that are broadly applicable across all types of cancers and therapies include (1) physical function, (2) disease symptoms, and (3) side effects and the impact of side effects (e.g., bother) (Fig. 21.1). It is recognized by the FDA OCE that distal concepts like social functioning and emotional well-being are important to patients, and possibly other stakeholders. However, when assessing the benefit-risk profile of an investigational therapy, there are non-therapy factors (e.g., satisfaction with care, family relationships) that contribute to these more distal concepts, which is why the results regarding these concepts are given less weight in the overall regulatory assessment [11, 12]. The notion of proximal and distal concepts was initially illustrated in the Wilson and Cleary model. This conceptual model of patient outcomes integrates both bio-medical and HRQL outcomes by describing five levels containing specific health concepts: (1) biological/physiological factors, (2) symptoms, (3) functional status, (4) general health perceptions, and (5) HRQL [13]. Health concepts 2 and 3 reflect where the OCE places their focus for PRO data. This is because the concepts falling under these broad headings have greater proximity to the disease and treatment of that disease. This is then ultimately reflected in what PRO label claims have been included by the FDA in the US prescribing information (i.e., the drug label). The EMA, on the other hand, has included the more distal and broader concept of HRQL in their drug labels for certain products (i.e., summary of product characteristics (SmPC)). The EMA has suggested that where the treatment is intended to be palliative as opposed to curative, the "focus of care is on promoting and preserving quality of life" [12]. The EMA advises that "in order to approve a global claim that a product 'improves HRQL,' it would be necessary to demonstrate robust improvement in

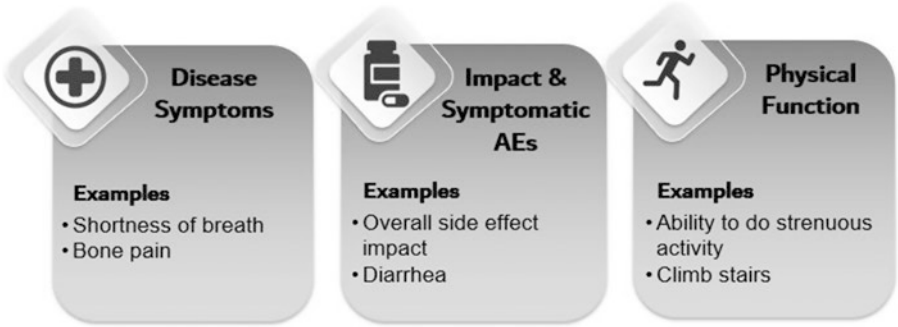

Fig. 21.1 Core Concepts of Interest to the US FDA Oncology Center of Excellence in Assessment of the Benefit-Risk of Investigational Therapies [15]

all or most of these domains" [6]. In line with this, in the new PFDD discussion document for guidance 3, the FDA wrote "For example, if improvement in a score for a multi-domain concept (e.g., symptoms associated with a certain condition) is driven by a single responsive item (e.g., pain intensity improvement) whereas other important items (e.g., other symptoms) did not show a response, a general claim about the multi-domain concept (e.g., improvements in symptoms associated with the condition) cannot be supported" [14].

More recently, the FDA has been encouraged via legislation (the 2012 Safety and Innovation Act [16] and in 2016 the twenty-first Century Cures Act [17]) to build on patient-focused drug development and include the patient experience in the benefit-risk assessment of new therapies when it has been collected, even when the data informs only exploratory endpoints. The FDA Office of Oncologic Diseases (OOD) has been successful in incorporating the patient experience into their reviews. As presented by Gnanasakthy, when there was patient experience data submitted as part of a New Drug Application (NDA) or a Biologics License Application (BLA), it was incorporated into the OOD's reviews 100% of the time since the twenty-first Century Cures Act was enacted [18]. However, there has been no change in the number of labeling claims based on PRO data since the introduction of the Cures Act. This is mainly because the trials that have read out their results since the Cures Act went into effect were designed at least 3–5 years prior to the legislation. This meant the PRO strategy was not prioritized, e.g., not included in the statistical hierarchy, for achieving a labeling claim.

In a published review of the inclusion of PRO claims in oncology drug labels, it was reported that of the 45 indications that included PRO data in the clinical trials, there were no oncology drugs that included PRO data in the US prescribing information between 2012 and 2106. This review, however, overlooked the approval of certinib [19] in 2014 and did not review label updates, which lead to exclusion of crizotinib, which received regular approval in 2013 without PRO data included in the label. However, an efficacy labeling change in 2015 lead to the inclusion of PRO data [20], highlighting how challenging it can be to track this information. The current US prescribing information includes PRO results for both these drugs. On the other hand, for the EMA it was found that 21 (47%) SmPCs where results from the analysis of the PRO data were included. As evidenced from the respective agencies' guidance documents this is to be expected as there are differences in the focus on how PRO data is incorporated into the benefit-risk assessment by the FDA and the EMA [21].

An example of the differences in how the FDA and EMA use PRO data in the label can be seen with the drug, ceritinib (Zykadia), approved for patients with metastatic ALK-positive non-small-cell lung cancer. In Table 21.1 the language from the FDA and EMA labels is presented

Table 21.1 Labeling Claim Language for Ceritinib (Zykadia)

Regulatory body	Year approved	Labeling language
US FDA [19]	2014	Exploratory analyses of patient-reported outcome measures suggested a delay in time to development of or worsening of "shortness of breath" in patients treated with ZYKADIA as compared to chemotherapy. The patient-reported delay in onset or worsening of "shortness of breath" may be an overestimation because patients were not blinded to treatment assignment.
EMA [23]	2015	Patient-reported outcome questionnaires (Lung cancer symptom scale [LCSS], EORTC-QLQ-C30 [C30], EORTC QLQ-LC13 [LC13], and EQ-5D-5L) were completed by 80% or more of patients in the ceritinib and chemotherapy arms for all questionnaires at most of the time-points during the course of the study. Ceritinib significantly prolonged time to deterioration for the pre-specified lung cancer-specific symptoms of interest of cough, pain, and dyspnea (composite endpoint LCSS: HR = 0.61, 95% CI: 0.41, 0.90, median time to deterioration [TTD] NE [95% CI: 20.9, NE] in the ceritinib arm versus 18.4 months [13.9, NE] in the chemotherapy arm; LC13: HR = 0.48, 95% CI: 0.34, 0.69, median TTD 23.6 months [95% CI: 20.7, NE] in the ceritinib arm versus 12.6 months [95% CI: 8.9, 14.9] in the chemotherapy arm). Patients receiving ceritinib showed significant improvements over chemotherapy in general Quality of Life and global Health Status measures (LCSS [$p < 0.001$], QLQ-C30 [$p < 0.001$], and EQ-5D-5L index [$p < 0.001$]).

(Table 21.1). In the US prescribing information from the FDA, the description of the results is limited in detail (e.g., no primary measures of interest such as point estimates, confidence intervals, or p-values). The FDA label also highlights that the analyses conducted were exploratory and may even be biased because of the trial design. The results presented focus on delay of onset or worsening of the symptom "shortness of breath," fitting with the use of concepts that are proximal to the drug effect. The description is also consistent with the advice provided by the FDA regarding inclusion of multiple endpoints, such that no point estimates are provided from *exploratory analyses*. Broadly speaking, the FDA, in their multiple endpoints' guidance, suggests that for an endpoint to be considered for inclusion in the drug label, the endpoint needs to be included in the endpoint hierarchy (i.e., prespecified and with multiplicity adjusted for). This is to overcome Type 1 errors, or in other words, false-positive findings [22]. Exceptions have been made to include exploratory analyses such as the current example for ceritinib, but the details presented in the drug label are generally limited. In the case of ceritinib, the information provided on "shortness of breath" comes from two randomized clinical trials. In both trials, the same conclusion regarding "shortness of breath" was drawn and the results were considered not to be a false-positive finding and therefore included descriptively in the US prescribing information.

On the other hand, the EMA included in their SmPC the point estimates, confidence intervals, and p-values. These results came from the delay of onset analyses, where the dependent variables were worsening of the symptom composite score from the Lung Cancer Symptom Scale as well as a composite score from the European Organisation for Research and Treatment of Cancer, lung module (EORTC QLQ-LC-13). In addition, in the EMA SmPC, improved QoL was reported for patients treated in the ceritinib arm.

The results presented in the FDA and EMA ceritinib label are not even from the same models described differently; the results are from completely different analyses. In the SmPC, the results are from time to event models, where the dependent variables are composite scores. For example, SmPC include the concepts of cough, pain, and dyspnea, whereas the results presented in the FDA label only address the concept of "shortness of breath." Though the names of the questionnaires are not provided in the FDA label,

both the LC13 and LCSS questionnaires include items that measure "shortness of breath"; therefore, the results could be either from instrument or from both with the same trend in the results. The EMA labeling text does not specifically address time to deterioration in the concept of "shortness of breath." The results are for composite scores, and from the SmPC alone, it is not possible to know whether cough, pain, and dyspnea were all improved in similar magnitude the treatment arm, as is suggested in the EMAs reflection paper on HRQL [6].

There is no single way to approach the inclusion of PRO results in a drug label though it could be argued that neither of these examples for ceritinib are ideal for health care providers and patients. While there are a few reasons for this, an important one is the result of there being limited standardization for PRO endpoints; with standardization comes the ability to summarize findings briefly. It is hard to imagine how this PRO information would be conveyed by a clinician to a patient. In the US prescribing information, there is no information on how long shortness of breath was delayed. In the SmPC, there is no information on whether all the symptoms in the composite were delayed or whether one or two of the symptoms led to increased delay. Later in the chapter we present a template for thinking about a standardized presentation of patient-reported symptom data and discuss the FDA OCEs pilot Project Patient Voice [24].

Examples of PRO Data Supporting Approval There are two examples in the US where patient-reported information was considered a marker of how patients feel, function and survive, and were part of the primary support for regulatory approval. In 1996, gemcitabine (Gemzar) was approved for "the first-line treatment of patients with advanced (nonresectable Stage II or Stage III) or metastatic (Stage IV) adenocarcinoma of the pancreas." In the pivotal trial, the primary endpoint was "clinical benefit response," a composite endpoint, which was defined by the trial sponsors as "based on analgesic consumption, *pain intensity,* performance status and weight change." More specifically, patients were considered to have a response if they "showed a ≥50% reduction in pain intensity (Memorial Pain Assessment Card) or analgesic consumption, or a 20-point or greater improvement in performance status (Karnofsky Performance Scale) for a period of at least 4 consecutive weeks, without showing any sustained worsening in any of the other parameters OR the patient was stable on all of the aforementioned parameters and showed a marked, sustained weight gain (≥7% increase maintained for ≥4 weeks) not due to fluid accumulation." The FDA reviewers acknowledged that "the clinical benefit endpoint measured in this study are "published and recognized as valid, reproducible, and reliable…"" [25]. However, this was the only time this novel endpoint was used for regulatory decision making.

The other example is for ruxolitinib (Jakafi), which was approved for the treatment of patients with intermediate- or high-risk myelofibrosis, including primary myelofibrosis, post-polycythemia vera myelofibrosis, and post-essential thrombocythemia myelofibrosis. The FDA decision was based on the reduction of both spleen volume and the six-item PRO measure total score of disease-related symptoms. The endpoint was defined as "The proportion of subjects who have a 50% reduction from baseline to Week 24 in the total symptom score" using the Myelofibrosis Symptom Assessment Form version 2 (MFSAF v2.0). The FDA noted in their review summary that this improvement is "potentially a direct measure of clinical benefit" and concluded that "These endpoints provide evidence of both a biologic effect of ruxolitinib and a direct patient benefit" [26].

Each of these clinical trials illustrate that there is potential for patient-reported information to support regular approval of new anti-cancer therapies. Use of PRO data was planned during the design and development of both studies. In the case of ruxolitinib, the sponsors requested a special protocol assessment, which led to the FDA agreement that the novel endpoint proposed in the protocol would be acceptable for consideration of approval. For PRO data, and really any

data collected during a clinical trial to be meaningful in the benefit-risk assessment of a new therapy, careful forethought is required to ensure that the design will answer the intended research question.

21.3 Efficacy Vs Safety/ Tolerability

The benefit-risk assessment of any new therapy recognizes there is, at times, a tradeoff between increased therapeutic benefit and increased risk of adverse events/toxicity, which is especially true in the evaluation of new oncology therapies. If the risk is acceptable given the benefit (i.e., the primary endpoint was met and the safety profile acceptable) of a new therapy, the therapy is approved. Data capturing the patient experience while on the clinical trial can be used in cancer drug development to answer questions about therapeutic benefit by way of efficacy hypotheses (e.g., ruxolitinib (Jakafi). The results are then presented in Sect. 14 Clinical Studies of US prescribing information) or questions about risk with respect to symptomatic adverse events (e.g., crizotinib (Xalkori), results presented in Sect. 6 Adverse Reactions of the US prescribing information) and tolerability.

In all advanced oncology trials, there is a place for the use of PROs to assess tolerability of the new therapy from the patient perspective because many common adverse events are unobservable (e.g., fatigue, nausea), making patient report a reliable means to understand these symptomatic effects [27]. The analysis of this data will likely be descriptive in nature, and care should be taken in the selection of an appropriate number of items. For example, while the National Cancer Institute's PRO Common Terminology Criteria for Adverse Events (PRO-CTCAE) [28] measurement system includes 124 items representing 78 symptomatic toxicities, the inclusion of all these items in a single trial is neither necessary nor good practice. As not all these items are needed in a single clinical trial, sponsors can work to identify a set of items that strike a balance between capturing relevant symptoms, avoiding ascertainment bias, and not over burdening trial participants. This can be achieved by using the free text option, and software is available where dropdown options populate with terms from the PRO-CTCAE library as well as MedDRA Lowest Level Terms [29]. The FDA OCE Excellence launched in 2020 a pilot project, Project Patient Voice, to provide a Web-based platform for healthcare providers to look at patient-reported symptom data collected from cancer clinical trials in order to discuss them at the point of care with patients and their caregivers [24]. The plan is to make this an option to cancer clinical trial sponsors to present their trial data when they have rigorously collected patient-reported symptom data. Efficacy endpoints, on the other hand, must be included in the endpoint hierarchy to be fully described in the US prescribing information. In a review of 25 lung cancer clinical trials used to support FDA drug approval between January 2008 and December 2017, no PRO endpoints were included in the efficacy hierarchy where type I error is controlled for [30].

Whether assessing an efficacy or safety research question, the objective and endpoint should be clearly described in the study protocol [31]. Also, the assessment frequency of a valid and reliable PRO measure should be appropriate for the endpoint. For example, if the treatment administration is intravenous infusion once every 28 days, asking patients to report their side effects over the past 7 days on day 1 of a cycle (i.e., 28 days after their last infusion) is unlikely to provide a realistic snapshot of the acute side effects that were experienced by patients. By day 1 of a new cycle, most side effects will have resolved. The most relevant time to ask may be around 5–7 days post-infusion, which would provide the most information for a safety/tolerability endpoint. However, typically the capture of PRO measures is tied to clinic visits, primarily to improve completion rates. This tradeoff between completion and optimal timing of the concept must be weighed, though electronic PRO measurement could in theory overcome the tying of assessments to clinic visits and can be done well, it is not without its own set of challenges [32, 33].

For example, if using the patient's own device, sometimes referred to as "bring your own device," there may be storage issues or updates to the operating system that can impact how PRO data is collected on the patients' own device that will require careful planning in the protocol.

21.4 What QoL Results Are Reported in the Literature

Primary clinical trial manuscripts describing the results of cancer clinical trials rarely include PRO results; however, there may be another manuscript published to describe the findings from the PRO data. In a literature review of PRO-focused manuscripts published between January 1, 2017, and December 31, 2018, it was found that while 93% of the papers reviewed included a PRO-related endpoint, only 33% tested a specific directional hypothesis [34]. In a systematic review of breast cancer clinical trial manuscripts published between January 2001 and October 2017 reporting PRO data, the majority of papers reviewed included a PRO endpoint. However, only 12% of these papers reported testing a directional hypothesis. The authors make an important point that the lack of a clear hypothesis can lead to the use of different analytic techniques that have the potential to lead to different conclusions. A clear research hypothesis helps in all stages from trial design to data analysis and finally to interpretation and translation of the results [8].

The results of PRO/HRQL analyses are often translated to a broad conclusion of no or small differences in HRQL or functioning between the clinical trial arms despite observing notable differential toxicity. An example of such a conclusion from a phase III randomized clinical trial of men with metastatic castration-resistant prostate cancer stated "mean changes from baseline in the FACT-P subscales were similar in both treatment groups, indicating that the addition of apalutamide to androgen deprivation therapy did not result in a decrease in HRQOL" [35]. This example is not intended to call out these particular authors, as Merzoug et al. found that 73% of the papers they reviewed came to the conclusion that the HRQL concepts assessed in the investigational arm were either better or the same as in the control arm [34]. In other words, the majority of the published conclusions reviewed had similar statements that study results favored the treatment arm or suggested equivalence between the control and treatment arms.

These findings could be related to a publication bias where only positive findings are accepted for publication. But there is also a methodological challenge here. Specifically, the challenge with conclusions indicating no difference or similar scores is that most clinical trials are not designed to test what is more formally referred to as an equivalence or non-inferiority hypothesis with respect to the PRO data [36]. What the authors are actually reporting is the absence of an effect or that the null hypothesis cannot be rejected. However, in trials that aimed to test superiority hypotheses (i.e., the investigational treatment is significantly and clinically better than the control arm treatment), we can only say that there *may be* no difference between the arms or that we did not have sufficient evidence to detect the difference when the test does not indicate superiority. There are several issues that arise in cancer clinical trials that must be considered and factored into the analysis and interpretation of absence of effect findings.

Two serious issues affecting the analysis and interpretation of PRO data are missing data and asymptomatic withdrawal. Missing data in cancer clinical trials is common. There can be missing items (i.e., items that a patient skipped) or missing assessments (i.e., the patient did not complete the PRO assessment and therefore no items were completed). Missing assessments are important to assessing data quality, and if not presented in the clinical study report, the FDA will likely send an information request to obtain the completion rates. Completion, in most trials, is defined as the proportion of on-study participants who were scheduled to complete a PRO assessment and filled in at least one question. While prevention of missing data is the best strategy, two low-burden actions that can be taken to improve interpretation in the face of missing data

were suggested in 1998 by Bernhard et al. [37]. First, collection of the reason for missing data helps researchers determine the mechanism of the missing data. For example, the EORTC uses the following reasons for missing assessments: patient felt too ill; clinician or nurse felt the patient was too ill; patient felt it was inconvenient or took too much time; patient felt it was a violation of privacy; patient did not understand the actual language or was illiterate; administrative failure to distribute the questionnaire; not required at this time point; other, specify; and unknown [38]. The other issue is that all clinical study reports could include the answers to the following three questions:

1. How many missing data were there?
2. Why were the data missing?
3. How might the missing data affect the interpretation of the results? [37]

Answering these three questions helps contextualize the PRO data findings. For example, if by month 3, only 60% of trial participants on either arm completed their PRO assessment, the generalizability of the results is limited. When the driver for missing assessments is sicker patients, this will likely lead to an overestimation of HRQL. Understanding why data are missing would further help regulators incorporate PRO findings into their benefit-risk assessment.

With asymptomatic withdrawal, it could be that in both arms 95% of participants who were scheduled to complete a PRO assessment did so, but that by month 6, only 30% of those randomized to the control arm remained on-treatment, whereas 70% of those in the treatment arm were on-treatment. This is problematic because in many trials PRO data collection stops when treatment ends. If PRO data collection continues post-treatment, it is often collected at less frequent intervals than while on study treatment and the quality of the data may be low (e.g., low completion rates). Asymptomatic withdrawal can introduce bias because there is only PRO data from the patients who were able to tolerate the control arm treatment and they remained on trial and the patients who experienced side effects or whose disease progressed withdrew earlier, and therefore, no PRO data was collected in the post-treatment epoch. This means that the PRO data is not missing at random [39]. One way to potentially mitigate this bias would be to pick a relevant time point in the treatment course where all patients complete a PRO assessment regardless of whether they remain on treatment or not and prioritize collection of that data.

Another important element for overcoming interpretation issues is pre-specification of well-defined PRO endpoints. In trials where PRO data is collected, the associated endpoint is not often detailed, for example, a frequently used endpoint is that *PRO data will be examined between the arms* [8, 40]. The Standard Protocol Items: Recommendations for Interventional Trials in Patient Reported Outcomes (SPIRIT-PRO) recommends that "Primary, secondary, and other outcomes, include the specific measurement variable (e.g., systolic blood pressure), analysis metric (e.g., change from baseline, final value, time to event), method of aggregation (e.g., median, proportion), and time point for each outcome" are included in the study protocol [31]. The largest barrier to this recommendation is that, as mentioned earlier, there are no standardized PRO endpoints for all cancer clinical trials. However, applying the estimand framework can help trial sponsors to structure their endpoints, including their PRO-specific endpoints. The estimand framework has been proposed by the International Council for Harmonisation and outlined in the E9(R1) addendum [41]. A detailed description of this framework is beyond the scope of this book chapter; however, the broad goal of the E9(R1) addendum is to align trial objectives, design, analysis, and interpretation. Finally, there is an ongoing multi-stakeholder project, Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium, that is aiming "to develop recommendations for standardizing the analysis and interpretation of patient reported outcomes and quality of life data in cancer randomized trials" [42]. This initiative includes regulatory agencies, payers, trialists, industry, academia, and most importantly patients, with the intended result

of standards developed using existing guidances and guidelines to help with the design of appropriate patient-centric endpoints as well as help to translate findings so that clinicians and patients can make sense of the results and use the results in shared decision making.

21.5 Disease and Treatment Context Matters

Most of the examples provided thus far have been trials that have supported approval of new treatments in the advanced stages of cancer. For many patients with early-stage cancer, there are few noticeable symptoms and diagnosis is made via screening efforts or due to clinical investigations related to another medical issue. On the other hand, patients with advanced disease may experience a greater number of disease-related symptoms. Therefore, just as we see disease-free survival, and not overall survival, used as a primary clinical endpoint in adjuvant trials, the PRO endpoints need to be different. For example, it may be reasonable in a trial investigating a new treatment for metastatic castrate-resistant prostate cancer to use a PRO endpoint where time to pain palliation is investigated [43]. This is because for there to be pain palliation, patients must start the trial with a certain degree of pain (usually >3 points on a 0–10 numerical pain rating scale) [44] and therefore baseline pain should be included in the inclusion criteria. In the adjuvant setting where patients are unlikely experiencing pain before treatment, it would not be possible to recruit patients into the trial. Patient-centric endpoints in the early-stage setting are an area that is continuing to develop. What remains the same though for both settings is understanding safety and tolerability of the investigational treatment.

21.6 Patient Perspective – Lee Jones

PROs are becoming more expected to be measured and reported in the clinical trial component of drug development. This is due on part to the requirements for "beneficence" in clinical trials, but also due to the importance of QoL considerations for patients on clinical trials as well as in post-approval clinical care.

The relationship between PROs and QoL is not always easy to determine. QoL is totally patient-centric, no two patients will consider the exact same experiences when asked to rate their QoL. This is because every patient is different in terms of sex at birth, gender identity, age, body structure, racial and ethnic background, genetic profile, and economic background among others. As a result, they will react differently to drug treatments clinically, emotionally, and intellectually. Clinical side effects can range from inconvenience to death. Emotional side effects can range from calm acceptance to clinical depression. Intellectual side effects can range from stoic acceptance to obsession. These differing reactions can result in differing pain thresholds and ability to accept and withstand whatever side effects they may be experiencing and will have a major impact on patients' real experience of symptoms and side effects, and their perceived impact on QoL. For example, diarrhea might be an inconvenience for a retired patient, but for a stage performer, it could dramatically affect their ability to work and thus negatively impact their QoL.

Patients will also differ in their short- and long-term objectives regarding their treatment. One patient may want to experience no treatment side effects, another may be willing to do anything to be able to live until their son's or daughter's wedding, and another may be willing to suffer anything for the best chance of long-term survival.

As a result of these differences, defining "quality of life" in a way that would apply to all or even most patients is very difficult. Most of what is measured today and that affect treatment decisions are clinical outcomes (e.g., laboratory values) for which the healthcare establishment has determined thresholds that are used to define "tolerability." This is even less relevant to many patients since clinical trials do not enroll patients that represent every combination of these individual characteristics so only when the drug is

approved for use in the real world is the real "testing" conducted.

Despite these considerations, QoL is a critical endpoint in the drug development process. Though the results will not be definitive and applicable to every patient, giving patients the range and scope of the factors that affect QoL will offer some comfort if and when they experience any of these same effects. Ultimately, it may be possible to give patients a "Chinese menu" of treatment options, with varying efficacies and side effects, so each patient can, in a shared decision-making process with their doctor, choose the treatment that will best take into consideration both the clinical effects of the drug and the feelings, goals, and needs of the patient. We have fleshed out a hypothetical example at the end of this section.

It is also likely that different data presentations of PRO/QoL concepts could be used, one set as part of the regulatory process, to measure the statistical difference between study arms and another set for patient decision making, where a different focus might be important, and the presentation of the data quite different. The former is primarily quantitative, the latter primarily descriptive and much more effectively presented visually so that patients do not need to understand statistics, for example, hazard ratios and 95% confidence intervals. An example of this might be peripheral neuropathy. For regulatory purposes, the CTCAE grade is important and how the proportions between treatment arms differ. However, for patients the grade may be less important, but knowing the length of time they might experience the symptom may be more significant—an intense, short-term bout may be of less concern than a milder but longer-term experience which might have a greater impact on their QoL.

One initiative underway that leads in the direction of presenting descriptive information is being undertaken by the US FDA. This initiative, called "Project Patient Voice," will show, using easy-to-understand graphics, the side effects reported by participants in clinical trials in terms of both timing and intensity of the effect [24]. Though currently limited to a demonstration of the approach, this initiative has the promise of offering patients the most realistic picture of what they might expect to experience when treated with the drug. In this way, each patient, in consultation with their oncologist, will be able to determine what combination of factors can result in the best (or least bad) side effects based on their unique set of attributes and perspectives. The process is still overly complicated to be able to be used by most patients and to be most useful to patients it would need to include information about patient characteristics, such as age, race, comorbidities, and tumor mutations as well as drug data related to efficacy, physical function, and PROs, so that a patient could better assess the effects of a drug on a "patient like me." This would become a massive database management and data collection, retrieval, and presentation issue that might be best handled with an artificial intelligence application.

Cancer patients need a better way to understand how the drugs available to treat their cancer will affect them, their cancer, and their QoL. Capturing PROs is a critical first step but the massive amount of data that is collected needs to be effectively managed and reported in a form that patients can understand and use in consultation with their oncologist to determine the best course of treatment for them. This would indeed make the promise of personalized medicine a reality.

21.6.1 Menu Presentation

In the face of a changing treatment landscape that has potential for multiple treatment options, understanding the tradeoffs between different side-effect profiles in light of efficacy findings would be useful for patients and healthcare providers. One could imagine a guide outlining benefits and risks of the approved treatment options next to each other for review as a shared decision-making tool (Fig. 21.2). Information regarding the patient's disease, including actionable mutations and biomarker information, could be fed in via a series of questions and this would pull from a database the relevant treatment options based

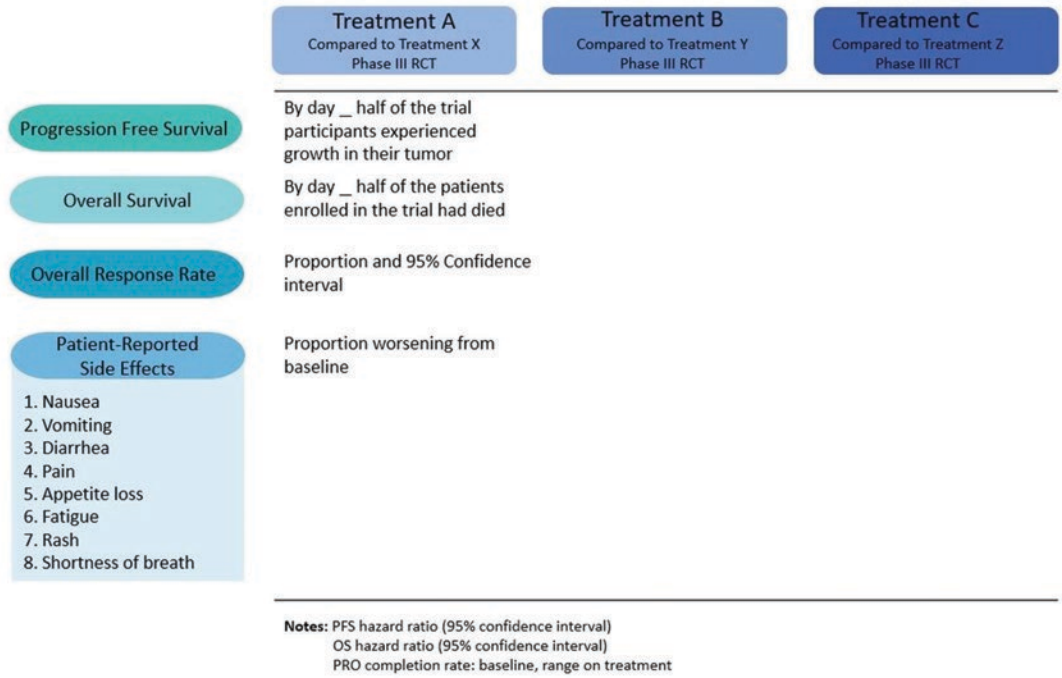

Fig. 21.2 Aspirational Menu Presentation of Clinical Trial Information

on the National Comprehensive Cancer Network Clinical Practice Guidelines.

The figure and description of our hypothetical shared decision-making tool is aspirational, and not currently possible to populate. Before such a tool can be developed, there are many challenges to overcome. However, one possible starting point is to leverage the data presented on the FDA's Project Patient Voice website once more trials are added. The symptom summary information presented in the table (worsening in symptoms from baseline assessment), as well as information on overall survival, PFS, and overall response rate (ORR) from the clinical trial, could be used to populate a tool like that presented in Fig. 21.2.

There are several limitations in relying solely on clinical trial data that need to be considered. For example, not all trials collect the same side-effect data, and this would leave gaps in the table because it might not be relevant to ask about hair loss in a trial comparing two tyrosine kinase inhibitors which are not known to cause hair loss. There is, however, a core set of side effects (anorexia, anxiety, cognitive disturbance, constipation, depression, diarrhea, dyspnea, fatigue, insomnia, nausea, neuropathy, and pain) that was arrived at via an NCI-supported consensus that could be routinely captured [45] but requires guidance from the regulatory agencies to be used more extensively. There are also challenges in comparisons of trial data. This is because the trial data can differ due to differences in trial inclusion and exclusion criteria. How these limitations would be incorporated as well as differences in the length of follow-up or missing PRO data need to be considered and a balance struck between sufficient description and too much description that could lead to difficulty to understand the important take away points. Clinical trial data is also not necessarily representative of the wider range of patients receiving treatment in the community. To overcome this, the table could be augmented with real-world data; however, at this time, PROs systematically capturing side effects are not commonplace in healthcare systems. Finally, the hosting and maintenance of such a tool is critical, and who should take on this role and how any related costs should be allocated are not clear.

But what is clear is that patients would benefit significantly by having a full range of efficacy and side-effect information so that together with their healthcare providers they could choose a treatment that best accords with their personal QoL and healthcare preferences.

21.7 Clinician Perspective – Lynn Howie

Patient-reported outcome measures can improve the data needed for clinicians and their patients to decide between therapies when disease-related outcomes are similar and there is no clear therapy that is substantially superior with respect to disease-related outcomes. Currently, we have very limited patient-reported data in FDA labels; however, as noted earlier, there are some key examples where this data has helped to inform the severity and duration of symptoms. Ruxolitinib, an agent for patients with myelofibrosis, was approved using a composite endpoint that included a radiographic endpoint of reduction in spleen size along with a reduction in patient-reported assessment of symptom burden as the primary efficacy endpoint for approval. Figure 21.3 is from the label describing the symptom reduction observed at week 24 [26] (Fig. 21.3). From these results, clinicians can advise patients that about half of the patients who receive ruxolitinib report that their symptoms are reduced by about one half after being on therapy for approximately 6 months. Crizotinib, an oral tyrosine kinase therapy for those patients with advanced lung cancer which has an ALK or ROS-1 mutation, is associated with ocular toxicities which can have a significant impact on patient function and QoL. In both examples, PRO data were used to characterize the frequency, duration, and impact of symptoms on patients' daily lives which can then be used to communicate benefit as with ruxolitinib and risk with crizotinib.

In choosing a therapy, patients and clinicians are interested in the side effects of treatment and how these will impact daily life. As we know, daily persistent symptoms can be more aggravating than more severe symptoms that are shorter in duration [46]. For patients who are continuing to work during treatment, it will be important to understand the impact of therapies on this aspect of their lives, as well as the impact on other daily activities such as exercise, ability to perform household tasks such as cooking and eating meals, and patient-reported experiences with symptomatic adverse events. So, questions that assess the impact on these areas will be most useful as patients and clinicians work to identify the best treatment for that patient when several options are reasonable.

Currently, we do not fully understand the patient experience of side effects and we even less so understand the impact on physical function and role function. We need to encourage drug manufacturers to include assessment of symptomatic adverse events and assessment of treatment impact on physical and role function in order to better understand the effect of therapy on patients' lives. This will help to provide patients and clinicians the data needed to make treatment decisions. In the current landscape of global clinical trials, it will also be important to understand how patient responses may be affected by the social and economic structures of the place where the patient lives. In geographical locations where there are robust social insurance programs that allow for the person to have job and/or economic security despite being unable to perform their job due to illness, the impact of side effects may be reported differently than in those places where the inability to perform job and other functions can have a more significant impact on patients' experiences.

21.8 The Future – What Role Can Real-World Data Play in Closing the Efficacy/Effectiveness Gap?

Both patients and clinicians are looking for representative data to help their patients make informed treatment choices. One path to that is

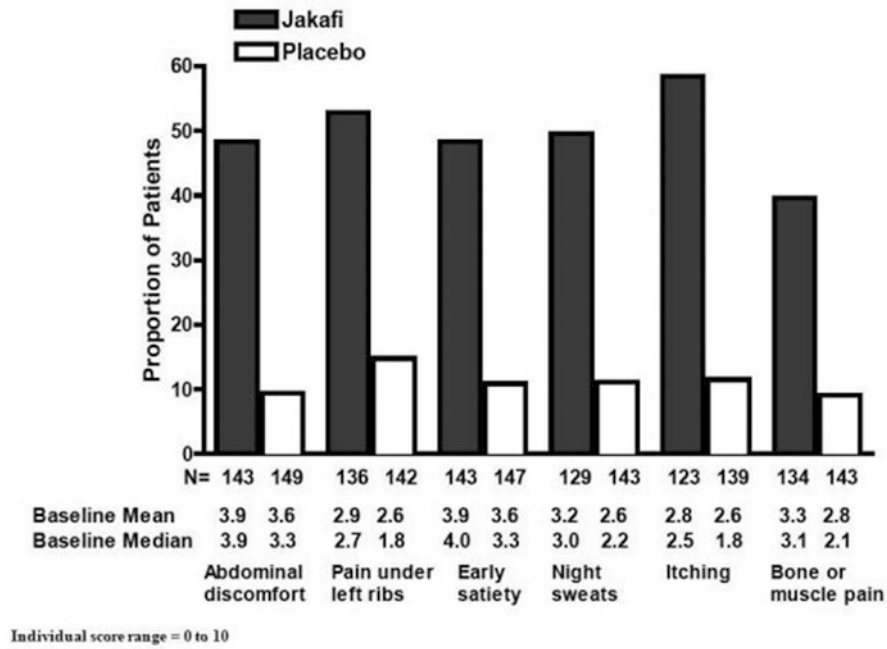

Fig. 21.3 Proportion of Patients with Myelofibrosis Achieving 50% or Greater Reduction in Individual Symptom Scores at Week 24

via the use of real-world data (RWD). This has been defined as "the data relating to patient health status and/or the delivery of health care routinely collected from a variety of sources. RWD can come from a number of sources, for example: electronic health records, claims and billing activities, product and disease registries, patient-generated data including in home-use settings, data gathered from other sources that can inform on health status, such as mobile devices" [47].

We are currently sitting at the forefront of the possibilities of real-world PRO data. This is because, at the moment, widespread implementation of routine collection of PRO measures in clinical practice is limited, which in turn limits the use of RWD for PROs. In a systematic review of the literature, the authors found that only 3 of 36 articles reviewed reported on implementation of PRO measures in clinical practice with the goal of managing patient care; the majority of papers reviewed were interventions that were carried out in clinical practice and used PROs to assess the success of the intervention [48]. This review may not reflect the true situation, as it is likely that more data is being collected than is reported in the academic literature. However, the collection of RWD that can be converted into real-world evidence (RWE) to support regulatory decision making and possibly close the efficacy/effectiveness gap starts with high-quality data collected in the clinic. Assessing the quality of that data and sharing of best practices is critical. The International Society of Quality of Life (ISOQOL) guidelines present some of the barriers to implementation into the clinic. These include resources, both procurement of equipment (e.g., tablet for electronic capture) and person power (e.g., establishing and sustaining the program). Beyond these challenges, other difficulties include standardization of collection of data and lack of best practices around the analysis and interpretation of the data.

To gain traction with RWD for PROs, straightforward questions and hypotheses are needed. RWD that describes the safety/tolerability of a new therapy may have the most immediate benefit, as these data can be used to better describe patient-reported side-effect experiences by subgroups (e.g., older age) of patients that look more like the patients regularly seen in the clinic. Also, many of the PRO projects currently center around symptom monitoring [48], meaning that there is existing infrastructure in place to capture this data. One of the issues that will need to be reconciled around symptom data collection for drug development is real-time monitoring versus passive data capture. Currently in industry-sponsored clinical trials, almost all PRO data collection is passively collected and not actively reviewed by the care team in real time. This is not always clear to patients enrolled in clinical trials [49]. However, PRO data captured to actively monitor and manage symptoms during routine cancer treatment has been shown to improve overall survival [50, 51]. Acknowledging the impact active monitoring may have will be an important consideration in the use of RWD that may be used to generate RWE.

21.9 Conclusion

In this chapter, we have touched upon many important issues for the inclusion of PRO measures to represent the patient's perspective in drug development and how that data can be applied in clinical practice. Many of the guidelines outlined within this chapter should not be taken to be prescriptive. Each study requires consideration of the specific treatment or study population and what research questions help inform the benefit-risk assessment of a new therapy. However, with careful planning of PRO endpoints, the results are interpretable and meaningful to all stakeholders, but especially to those who have been diagnosed with cancer and want to make informed choices.

21.10 Questions That Can Be Used for Learning/Testing

- When planning a trial that will be part of a licensing application, what patient-reported concepts are most relevant and why?
- What are the key considerations for timing of patient-reported assessments when planning the schedule of assessments?
- If planning to include a PRO label claim, what are the key considerations for the inclusion of PRO data in the drug label?

21.11 A Topic for Discussion That can Be Used for Teaching

- What are the possible implications for reporting different PRO results in the US prescribing information and the European summary of product characteristics?

21.12 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

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21.13 Research in Context

An important manuscript where the authors reviewed the advanced breast cancer randomized clinical trial literature between January 2001 and October 2017, with the aim to examine the types of analyses that were used for the PRO data collected and published in this peer-reviewed literature. The authors' search led them to review 66 papers. From these papers, it was determined that only 12% of papers presented a predefined directional hypothesis that they set out to test with the analyses conducted. Over half of the papers (58%) investigated multiple domains from the questionnaires used, though only 16% used a statistical adjustment to correct for multiple testing. Nearly a quarter (23%) of papers presented a p-value, indicating some types of comparative analyses were conducted, but did not report the type of analyses that were used to obtain the p-value(s). Most papers (73%) did not report how missing data were handled, which is critical as missing data is a key issue when analyzing PRO data from randomized clinical trials. Completion rates at baseline were presented for 47% of papers, and for the period where patients were on study, only 29% of papers included completion rates. Pe et al. provide the following example of how missing a hypothesis, one of the most fundamental steps of conducting a clinical trial, can impact the results: "if a study aimed to measure HRQL changes over a 6-week period, a cross-sectional HRQL analysis at 6 weeks is not equivalent to an area under the curve analysis within the same timeframe; in fact, these two analytical techniques could yield different results." Because there are no standards with how PRO data are analyzed and reported from clinical trials, the results from this study are not surprising. However, this work was carried out as a part of the Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data for Cancer Clinical Trials (SISAQOL) consortium, which will address this exact problem over the coming years [8].

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Part IV

Case Studies of Using Quality of Life Tools for Specific Cancer Types

Quality of Life in Breast Cancer

22

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Contents

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22.1 Introduction

Breast cancer is the commonest female cancer. According to global cancer statistics, in 2020, more than 2 million patients were affected by this disease [1]. Worldwide, there are currently millions of women that are either undergoing treatment or have survived from their disease.

The median age of breast cancer patients is around 60. One in eight women will be diagnosed with breast cancer during their life span.

Despite the anxiety seen in younger women, the incidence of breast cancer in the younger population is much lower (Fig. 22.1). Nevertheless, one could argue that the impact of this disease on the younger patient groups is more profound, as it is affecting a major part of the workforce, it is affecting parenthood, partnership, relationships and social stability.

Nowadays, breast cancer is the leading cause of death in women less than the age of 50.

So, what is the cause of this otherwise common disease? What is our answer to this young and healthy patient who walks into our clinic with a diagnosis of breast cancer? Why me doctor? What have I done wrong? What have caused my cancer? For the majority of our patients there is no answer, as breast cancer is a multifactorial disease with many risk factors involved.

This chapter will enable readers to familiarize their selves with this very common disease, analysing risk factors, current management options, and how all these treatment options affect the quality of life of the patients.

22.2 Risk Factors

One of the strongest risk factors is age. It is clear that the aging breast has more chances to be affected by mutations causing neoplasia. Aging and prolongation of life are the prices societies are paying to carcinogenesis [2].

There are many other risk factors that play an important role in breast cancer development [2, 3]. The exposure to radiation at a younger age, as

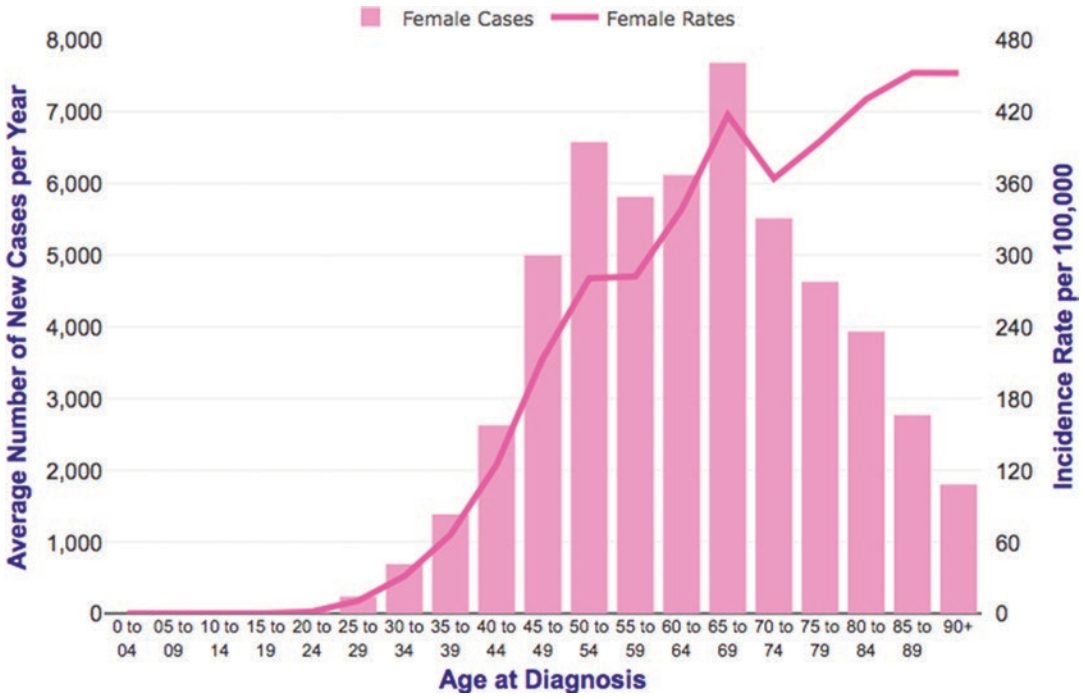

Fig. 22.1 Breast cancer (C50), average number of new cases per year and age-specific incidence rates per 100,000 females, UK, 2015–2017. Breast cancer research UK

part of treating an underlying malignancy, is a significant risk factor, with the anticipated risk of developing breast cancer 10 years post the completion of radiation being significantly higher compared to that of individuals with no radiation exposure.

External hormonal treatment is another risk factor, and many studies have shown that prolonged exposure to HRT (hormone replacement treatment) increases the risk [4]. As the exposure of the female breast to longer hormonal manipulation has been shown to increase the risks of neoplasia, it is clear that early menarche and late menopause are also among the risk factors.

Genetic factors are among the contributing factors and despite the fact that they exist in less than 10% of the patients, their role is clear. Genes like the BRCA1 and BRCA2, located in chromosomes 17 and 14, when mutated, increase the risks of patients significantly. Patients with BRCA1 and 2 have a lifetime risk of developing breast cancer that could be up to 70% [5]. Other genes like PTEN, CHEK2, p53 are also associated with breast cancer and other malignancies, such as ovarian carcinoma, brain tumours and pancreatic disease.

In recent years, obesity, the 'disease' that has become a pandemic in the Western societies, has been associated with postmenopausal breast cancer. Alcohol consumption is one of the newest environmental and dietary associations with breast cancer. There is nowadays a clear dosage level of alcohol consumption and breast cancer risk increase [6].

Other risk factors like previous benign breast disease [7], history of previous trauma and increased breast density, as seen on mammography, have also been recognized.

22.3 Treatment of Breast Cancer

Once the diagnosis of breast cancer is made, the patient will undergo treatment that today incorporates surgery, radiotherapy, biological agents, chemotherapy and hormonal treatment. What have changed in the last decade is the individualization of cancer treatment and the recognition that better survival comes with expertise and multidisciplinary approach [8].

Since the discovery of the different molecular profiles of breast cancer and the publication by Peru [9], we know that every patient fits a different disease model and the approach and the sequencing of the treatment vary significantly, depending on the molecular profile of the tumour. We have today recognized at least four different subtypes of breast cancer like Luminal A, Luminal B, her-2 enriched and triple negative. Depending on this profiling, patients might have a completely different approach and disease outcome is different. As an example, patients with her-2 enriched breast cancer, or triple negative will today be offered chemotherapy prior to surgery (neoadjuvant approach), and that will be followed by surgery and then radiotherapy. Hormonal-driven breast cancers remain the commonest group in all ages, and within this group there is the tendency of offering less chemotherapy with the help of the genomic and prognostic assays. Every single breast cancer patient that presents in the oncology clinic is unique, and any treatment intervention should be decided by the multidisciplinary team that includes radiologist, medical and radiation oncologists, histopathologists, breast and plastic surgeons. All patients should have an initial core biopsy that defines their molecular subtype before any decisions about further treatment are taken.

22.4 Modalities of Breast Cancer Treatment

22.4.1 Surgery

Surgery remains one of the most important treatments in breast cancer. Throughout the years, surgery has moved from the very radical and mutilating approaches of total mastectomies with removal of the whole breast and the muscular structures, to less invasive and minimal surgery. Depending on the size of the lump, the majority of patients today will have conservative surgery with minimal surgery in the axilla. The axillary clearance, which is surgery to remove a signifi-

cant amount of lymph nodes from the axilla, will be offered only to patients with significant volume of involved nodes in the axilla. Today the most standard surgical approach in the axilla is the removal of the sentinel lymph node, the 'guardian' node of the axilla, or the targeted axillary clearance in patients with a small number of metastatic nodes. This approach spares patients from the future development of lymphoedema and aims to avoid post-surgery deformities in the breast area and the axilla.

If mastectomy is needed, reconstructive options, either with implants or autologous grafts, have significantly improved the cosmetic outcome. Patients nowadays, in contrast with the past, will be given the option of immediate reconstruction during the breast cancer surgery.

22.4.2 Chemotherapy

Chemotherapy remains one of the most stressful treatments around malignant disease. Any new patient that walks into an oncology centre will have the fear of chemotherapy, which is associated with the fear of hair loss, nausea and fatigue.

Chemotherapy is mainly offered to very young patients, patients with more advanced nodal disease or patients that have special breast cancer subtypes like triple negative or her-2 enriched. In recent years, molecular profiling of the tumours especially the ones that are oestrogen receptor positive, have added tremendous assistance in the correct identification of the cohort of patient that will have a gain from the adjuvant chemotherapy, thereby avoiding overtreatment of patients with a favourable tumour profile.

Chemotherapy remains one on the main treatment options in patients with metastatic disease.

22.4.3 Biological Agents

The major innovation in treating malignant disease during the last 2 decades has come with the discovery of the molecular subtypes and the use of the targeted monoclonal antibodies. Breast cancer and haematological malignancies have been the pioneers in the use of targeted treatments in neoplasia, completely changing the traditional treatment field in cancer care. Since the FDA approval of Trastuzumab in 1998, newer biological agents have been approved, not only in breast cancer but also in lung and bowel malignancies, improving considerably the overall survival of patients.

Nowadays, in a breast oncology clinic, there is a number of new anti-her-2 agents, immunotherapy for the triple negative tumours and cyclin-dependent kinases, CDK 4/6, for the advanced metastatic ER positive breast cancer. All of these agents have been associated with improved survival and disease-free survival (DFS) in the adjuvant and metastatic setting.

22.4.4 Radiotherapy

Among the oldest and commonest cancer treatments, widely used in breast cancer, radiotherapy has also seen considerable improvements in the recent years with the application of shorter courses over few weeks compared to the more prolonged regimes of the past. Modern radiotherapy planning techniques with the incorporation of better imaging equipment, like CT scan and MRI, have helped in improving the cosmetic outcome but more importantly in avoiding unnecessary toxicities to the surrounding healthy structures.

22.4.5 Hormonal Treatment

Hormonal treatment remains the cornerstone of the treatment of the ER (oestrogen receptor) positive group. In a proportion of patients in the adjuvant setting, hormonal treatment has been prolonged to up to 10 years. Women will either be offered Tamoxifen an ER modulator, or aromatase inhibitor, like anastrozole, letrozole and exemestane.

Despite the major advances in disease understanding and the major and innovative treatments that have been used, not only in the early stage of disease but also in the metastatic setting, a per-

centage of breast cancer patients will relapse during the course of the illness and will succumb from the disease.

Through this long patient journey from the initial diagnosis, the initial emotions of the patient facing the new breast cancer disease, the treatment journey, the prognosis and its risks, one has to try and maintain one important aspect: quality of life.

For this complex disease, quality of life has to be measured not only around the patient but also around its carers and the environment.

22.5 What Is Quality of Life?

Although frequently used today, quality of life is not that easy to define (see also Chap. 1, this volume). As per WHO, it is 'the perception of an individual of their position in life in the context of culture and value system and in relation with their goals, expectations, standards and concerns'.

Patients with breast cancer will be faced with many challenges throughout their prolonged journey with the disease. Comparing breast cancer with other malignant disorders, one needs to realize that there are major challenges and major differences. Hormonal-driven breast tumours (the commonest group) have a very good 5-year survival, but they still maintain a small but real risk of relapse for the rest of the life of the patients, making the need for prolonged drug treatment. This is almost unique for this disease. Unfortunately, this disease is so heterogenous that quality of life might be completely different from one breast cancer subtype to another.

We will analyse in points all these challenges of the different treatment approaches offered in breast cancer and how these factors influence the quality of life.

22.6 Age

Life challenges and quality of life are different for an elderly breast cancer patient when compared to a younger individual. Challenges will always be there, but the impact on living with a serious and chronic disease can be different across lifespan [10]. Younger age was one of the major sociodemographic characteristics associated with distress on a systematic review from 42 studies published in 2017 [11]. A patient with a young family and young children, a patient planning to start a family and a young professional have many challenges to face when embarked with the cancer diagnosis. Suddenly there is the need of postponing, or even halting current plans, reviewing relationships and family roles. A mother of two with a full-time job might struggle to go through a 6-month chemotherapy treatment. Struggling will not only be because of financial difficulties, but also because career might be put on hold, job and travelling opportunities need to be adjusted. For very young patients, their family planning process will also be affected, they will review their interpersonal relationships, they will have fear for the risks on their fertility from the ongoing treatments. Breast cancer treatment can change body image, affecting sexuality. Marital strain is not uncommon and alienation from society with depression are often observed.

Sexual dysfunction is also common [12]. A high percentage of patients reported sexual dysfunction not only when they were receiving treatment but also after the completion of treatment [13]. In many societies, discussing sexual dysfunction remains a taboo. Even in more advanced societies, patients and healthcare professionals infrequently bring up the issue of sexuality. This is most of the times superseded by other stressful toxicities a patient might report during the clinic visit.

Is the sexual dysfunction associated only with the fear of the new and life-threatening diagnosis? Although the psychological issue is one factor, another important factor is the toxicity associated with the treatment patients are undergoing. Chemotherapy causes early menopause with associated vaginal dryness and loss of libido. Similar toxicities are frequently seen with the use of the hormonal treatment either alone like Tamoxifen or AIs (aromatase inhibitors) or in association with LHRH agonists. Hormonal

treatment causes dryness, amenorrhoea, dyspareunia and poor performance in sexual life.

A third important factor affecting sexual life is surgery, and it seems that any form of surgical intervention to the breast can have a negative impact on sexuality. Surgical treatment entails physical changes to the body that can have adverse effects on the patient, affecting mainly intimate relationships. There is a reduction in the self-perceived attractiveness following mastectomy with negative impact on sexuality. Despite the fact that breast conserving surgery offers better aesthetic outcome, it seems that any form of surgical intervention can affect sexuality. It is vital to discuss all the issues of surgical treatment with the patient so they have a better understanding on what it means to their body, helping them to have acceptance of their new look.

What about quality of life in the elderly patients? In this group, other issues need to be addressed [14]. Struggling with even simple things, for example, cleaning, cooking, looking after an elderly partner could create major stress. The adjustment to the new reality of the disease can be more difficult, and depression and suicidal thoughts are common with advancing age.

QoL in elderly seems to be worse when offering chemotherapy. Chemotherapy toxicities are more profound, and there is evidence that there is a drop in their QoL [15]. Old age is associated with other comorbidities, and older patients are often receiving concurrent medication, thereby making the score of QoL from cancer treatment difficult.

Old age might be a factor for not offering all the best possible treatments, and this is why the incorporation of geriatric assessment tools [16] is important when discussing cancer treatments in this population. Unfortunately, elderly people are sometimes offered less treatment, as, until recently, they were excluded from many clinical trials.

22.6.1 Age and Fertility

Child-bearing has changed considerably over the last few decades, with couples postponing the initiation of family. It is therefore not uncommon for any young breast cancer patient walking in the clinic not to have children. Not only do breast cancer treatments affect fertility but the diagnosis itself demands postponing any pregnancy plans to a safe time frame of at least 2 to 3 years from the initial diagnosis, depending of course on many patient and disease factors [17]. This is a considerable progress from the past when pregnancy was almost forbidden post cancer diagnosis, or was only allowed after many years of being disease free.

Nevertheless, fertility post cancer treatment is not guaranteed, and this is why appropriate counselling of the young woman is vital as she will need to be given the option of fertility preservation. There is enough data to suggest that this is another stressful event that compromises quality of life in this group [18].

22.6.2 Stage of Disease

The stage of breast cancer is associated strongly with disease prognosis. Disease stage is an independent factor of poor quality of life across ages. The number of involved lymph nodes at presentation associated with more advanced stage disease was associated with depression and anxiolytic prescription [11]. During the course of this disease, patients will have the anxiety of surviving. One of the most important aspects of patients' psychology is to educate them to accept their disease, and to also accept the small risk of developing metastatic disease. Having a breast cancer diagnosis today at an earlier stage with the help of the screening, patients need to realize that their prognosis in early stage remains very good. It needs though enormous mental discipline from the patients to bypass the fears of the disease and to continue living life as normal.

And what if the cancer is back, and what if suddenly in a clinic environment the patient is given the bad news of disease progression, disease relapse, disease metastasis, or even found to have metastatic disease upfront [19]. For any patient, this terminology is irrelevant! Of relevance is now the realization that metastatic breast cancer in 2020 remains an incurable disease.

It is a fact that progress has been made, and 30% of this group will manage to live for more than 5 years. But what quality of life assessment tool will capture this fear? Most probably none! The sadness, the panic, the vulnerability and the fear of a disease that could cause disabilities are emotions encountered frequently in the metastatic setting.

And indeed, when we assess quality of life in early breast cancer, there are many tools and the consensus is easier. In the metastatic setting though quality of life is less clear, here progress needs to be made.

There is enough data to suggest that women with metastatic breast cancer will have reduction in their quality of life not only because of the fear of death from their incurable disease but also, as they move through the combination of palliative treatments, they will experience fatigue, neurotoxicity, neurocognitive impairment, etc. Every effort should be made in assessing the needs of this special group of patients and try to offer support. Patient-centred communication and shared decision-making between any metastatic patient and the physician are vital. There are many patients' stories on how they handle the fear of death. This fear as expected is different among different ages.

22.6.3 Breast Surgery and Breast Reconstruction

22.6.3.1 Mastectomy and Breast Conservative Surgery

For the majority of the patients, wide local excision with breast conservation remains the standard approach. For a number of reasons, a patient might be offered mastectomy instead of wide local excision. Multifocality, very large central tumours, inability of the surgeon to achieve clear margins, very young age and genetic predisposition are among the commonest reasons for offering mastectomy.

Breast reconstruction post mastectomy has improved considerably over the last decade, and nipple- and skin-sparing mastectomies are frequently offered, achieving excellent aesthetic results.

There is enough data to suggest that women that have undergone mastectomy score lower in their quality of life. Body image, future perspective and also acceptance of the systemic treatment toxicity were worse in the mastectomy group in accordance to a recently published meta-analysis [20]. As expected, there are limitations in the analysis as many factors could play a role, that is, mastectomy was associated with larger tumours, therefore worse prognosis, so any impairment of the quality of life might have been due to stage of the cancer and not the type of surgery! There is a universal acceptance though, that the less surgery is done, either in the breast or the axilla, the better the cosmetic outcome, and that will extrapolate to a better quality of life.

Plastic reconstructive options have improved nowadays, but the fear and the acceptance of the new body could be difficult among patients. Even with the better reconstruction, patients might run into problems with the implants with capsular formation post radiotherapy or pain associated with surgery. Immediate breast reconstruction (performed at the same time as the initial breast cancer surgery) was associated with better quality of life compared with the delayed option.

There is a trend nowadays for younger women to request more mastectomies even on the healthy breast as the fear of the initial diagnosis, and the fear of future relapses make the radical approach extremely appealing. Clear discussion with the patient regarding the post-surgery quality of life should always be raised at the initial consultation therefore enabling the patient to make the correct decisions judged by scientific facts and not emotions.

Another factor that has improved considerably is the surgery done for the axilla.

Surgery has moved from axillary dissection with removal of a large number of nodes to minimal axillary surgery and removal of the sentinel node.

Even with this minimal surgery, a significant percentage of patents will suffer from lymphoedema. It is estimated that up to 30% of breast cancer patients might suffer with lymphoedema pain and arm swelling. Quality of life is impaired as lymphoedema is a debilitating condition with a long-term negative impact on a patient [21].

22.6.4 Hormonal Treatment

Hormonal treatment is a major component of breast cancer treatment with the majority of the women having to take it for a prolonged period of time. Five to 10 years of either Tamoxifen (mainly used in the premenopausal women) or aromatase inhibitors (first choice in the postmenopausal group) are the standard of care for all Luminal A and Luminal B breast cancer subtypes. A big percentage of all breast cancer patients either with early or advanced disease will be offered a form of hormonal manipulation at some point during their treatment.

Toxicity profile differs among the antioestrogens like Tamoxifen, and the aromatase inhibitors like letrozole and anastrozole.

Tamoxifen causes hot flushes, weight gain, mild hair loss and mood swings, whereas the use of AIs is associated with bone and joint aches, raised lipids, hot flushes and osteoporosis. Vaginal dryness is commoner in women on AIs compared to Tamoxifen.

Drug adherence could be compromised as these group of drugs need to be taken for long, and sometimes patients are abandoning them without informing their physician.

Few reports have exclusively analysed the quality of life with the use of hormonal treatment, but it seems that there is a compromise and reduced quality of life.

Antioestrogens might affect the mood of patients and compromise their libido and sexual function. Drug adherence could be compromised as these group of drugs need to be taken for long, and sometimes patients are abandoning them without informing their physician. The negativism around taking a treatment that might cause a young patient to dive into menopause, might lead to a disturbed doctor-patient relationship, as there is enough data on patients not taking their treatment but never reporting it!

Aromatase inhibitors are prescribed in up to 60% of patients and prescription is increasing, as there is an increase in their use among the premenopausal group. Musculoskeletal toxicity is well documented and indeed a percentage up to 50% will report joint and muscular pain within a year of use. This is a contributing factor on the lower QoL seen with this class of drugs [22].

Beyond the oral treatments, younger patients with higher risk disease will be offered a gonadotrophin-releasing hormone agonist (GnRHa) on a monthly basis, for up to 2 or 5 years in conjunction with their oral treatment. GnRHa is a monthly subcutaneously administered treatment that is offered to many premenopausal patients, in accordance with the results of the SOFT and TEXT study suggesting a benefit to the premenopausal hormone receptor positive higher risk group [23]. With this treatment, an immediate effect of castration is seen in this younger group changing their hormonal status from premenopausal to postmenopausal. Handling of the menopausal symptoms that appear in such an abrupt way could be difficult especially in the younger groups.

22.6.5 Chemotherapy Treatment

Chemotherapy is commonly offered to younger women with the disease, and it is a major part of the treatment in the metastatic setting. Among all cancer treatment modalities, chemotherapy remains the most fearful of all.

From various studies, it seems that quality of life is compromised during and after chemotherapy. Not only does the patient have to deal with its own fear of the unknown pathway of chemotherapy, there is anxiety about the future, anxiety about the impact of chemotherapy on the rest of their family, like children and spouses. While a patient is receiving chemotherapy, abandonment of routines might be seen. Patients might need to modify their work activities, and they might be off sick from their work environment for a while with social and financial consequences.

Chemotherapy is associated with acute treatment toxicities seen when the patient is receiving the treatment, and late toxicities that appear months to years from the completion of treatment. Among the acute toxicities, nausea, vomiting and myelosuppression are seen within days of offering the treatment. Hair loss is a common side effect in breast cancer patients as the cytotoxic agents commonly used are anthracyclines and taxanes, agents with high incidence of alopecia. Appearance-related side effects during che-

motherapy especially the hair loss, the loss of eyebrows and eyelashes could have a negative impact on social engagements and could compromise the quality of life [24].

Long-term toxicities from chemotherapy are not negligible, and they are associated with a small cardio toxicity risk, infertility with gonadal suppression and small risk of secondary malignancies. Other long-term toxicities that are extremely important have to do with the neurocognitive impairment, with the condition referred by patients as 'chemo brain', an entity that has been clearly reported and documented. As per the American Cancer Society, 'chemo brain' is a decrease in the mental 'sharpness' seen post cancer treatment. In science, it is defined as cancer-related cognitive impairment (CRCI) and includes impairment of short-term and working memory, attention, executive function and processing speed. Some of the toxicities can be difficult to go through, and sometimes they appear at the completion of the treatment or years later. Up to 50% of breast cancer patients will report this CRCI, and it can be a cause of distress to the patients as it can impair their day-to-day activities [25].

22.7 Type of Cancer

Little is known about the influence on quality of life among the breast cancer subtypes and the analysis on this is less clear. In the majority of the published data, the analysis on breast cancer is done with breast cancer been mentioned as one unique disease. Having the clear recognition of the breast cancer subtypes, their different treatment pathways, different chemotherapy and monoclonal antibodies and clearly different survival, we do expect to see in the future more analysis on quality of life based on the molecular tumour characteristics. Triple negative breast cancer and her-2 enriched are the two subtypes that women are commonly offered chemotherapy. Most of the times, patients with these two groups present with larger tumours [26]. Patients with these two subtypes have increased anxiety as they are aware of the more complex treatment options. The fear of negative future perspectives is very high and reduced quality of life with anxiety regarding the prognosis and treatment that accompanies the patient. There are reports on the anxiety caused by the finding of a less favourable breast cancer type, like triple negative. Inevitably patients will associate the certain breast cancer subtypes with the worsening prognosis and that will compromise their quality of life.

22.8 Carers and Environment

Any new diagnosis of cancer, and the treatment that will follow, creates a major stress not only for the patient but also for their carers. Adaptation to the new diagnosis of a chronic disease is not merely to the patients but affects spouses and extended family environment. The carers involvement in all aspects of the patient's treatment from the early stage of disease to the end-of-life care can be diverse and could also be influenced by cultural differences around the globe. Negative effects from the cancer treatment are experienced not only by the patient but also by its carers in a form of dyadic effect [27]. Understanding the carers needs in a breast cancer clinic could be challenging. In recent years, more attention has been paid in the carers needs, as a more holistic environmental approach will empower both the patients and their caregivers.

The fear of metastatic disease affects enormously the patient's environment and his/her carers and does so in amplified way compared to the early stage of the disease. There is lack of data on the impairment of quality of life on the carers of patients with incurable disease as the patient remains at the centre of the oncologist's attention, but it seems that caregivers report higher distress and less quality of life [28].

Scoring the emotions of the carers can be extremely hard. Emotionally they have to deal with fear of the loss of their loved ones. Beyond their emotional stress, the depression and anxiety they experience, they are also faced with physical and social stress. As they provide physical help to the patients, they might experience fatigue, lack of sleep and exhaustion [28]. There is increased anxiety around social circumstances, upbringing of offspring's and financial concerns.

22.9 Conclusion

As breast cancer is the commonest disease seen today in women and as it is one of the leading causes of death, scientific forces should be directed in offering new and pioneer treatments that will help prolonging the life of the patients. The ultimate target should be to cure this disease achieving longer survival and almost zero deaths. As with any other malignant disease, preservation of the quality of life in a holistic approach should walk alongside any treatment interventions. Throughout the spectrum of the ages affected, there are different concerns around the treatment options and associated toxicities. The ultimate goal should be to identify all the different treatment options offered in this heterogeneous disease during the lifespan of patients and act proactively so quality of life is maintained. High-quality research is needed in an attempt to improve holistically the life of breast cancer patients.

22.10 Questions That Can Be Used for Learning/Testing

1. Breast cancer affects women during their lifespan. What are the challenges faced among the different age groups affected by the disease?
2. What are the different molecular subtypes of breast cancer and how treatment gets differentiated?
3. What are the surgical options in a patient with a new diagnosis of breast cancer?
4. Quality of life in carers. A new topic with many challenges.
5. Sexual dysfunction in association with hormonal treatment.
6. Which genes are affected in breast cancer?

22.11 A Topic for Discussion That Can Be Used for Teaching

As survival in metastatic breast cancer is increasing with innovative new treatments, the social consequences of living with metastatic disease are enormous. Work environment, work absences as a result of treatment and toxicities, financial insecurities, cost of new treatments, raising up a young family, relationship and many more are all put aside, as patients and medical teams need to concentrate on the metastatic disease. What actions societies, patients advocate groups, policy makers and medical teams should undertake to try and improve in a more holistic approach the quality of life of the breast cancer patients beyond the actual medical treatment?

22.12 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

- Nardin S, Mora E, Varughese FM, D'Avanzo F, Vachanaram AR, Rossi V, Saggia C, Rubinelli S, Gennari A. Breast Cancer Survivorship, Quality of Life, and Late Toxicities. Front Oncol. 2020 Jun 16;10:864. doi: https://doi.org/10.3389/fonc.2020.00864. PMID: 32612947; PMCID: PMC7308500.
- Invernizzi M, Kim J, Fusco N. Editorial: Quality of Life in Breast Cancer Patients and Survivors. Front Oncol. 2020 Nov 18;10:620574. doi: https://doi.org/10.3389/fonc.2020.620574. PMID: 33312961; PMCID: PMC7708334.

22.13 Research in Context

Despite the realization that quality of life is among the most important factors in malignant disease, there is not a uniform tool to measure it. The different treatment options offered to breast cancer patients and their different molecular patterns make identification of factors that cause distress extremely difficult. The publication by Syrowatka et al. from Canada in Breast

Cancer Res Treat, in 2017, identified a large number of articles published in literature examining causes of distress in breast cancer patients. Only 42 studies were eligible and collected from the period of 2001 to 2016, either using a prospective cohort, retrospective chart review or they were with a cross-sectional design. The majority of the studies measure depression, anxiety, posttraumatic stress disorder and general distress. The most commonly evaluated predictors were related to breast cancer characteristics, patients' sociodemographic features and treatment-related symptoms. As anticipated on the analysis of breast cancer characteristics, the more advanced cancer at the initial diagnosis and treatment with chemotherapy were associated with distress. Sociodemographic features of younger age, being single and being from lower socioeconomic status were associated with reduction in quality of life. Analysing the treatment-related effects, menopausal symptoms that appear post cancer treatment, pain, fatigue, sleep disturbances and lymphoedema were also associated with distress. As with other studies around quality of life, there are limitations and indeed the authors conclude the need of assessing a larger cohort of breast cancer survivors prospectively to identify distress using time-to-event analysis. Survivorship-related issues in breast cancer are common, and with this systematic review a set of evidence-based predictors could identify the population that is at higher risk and offer them the support they will need in their long survivorship journey [11].

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Quality of Life and Brain Cancer

23

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23.1 Introduction: Brain Tumours

In 1926, Percival Bailey and Harvey Cushing published their book *A classification of the Tumours of the Glioma Group on a Histogenetic Basis with a Correlated Study of Prognosis*, in which the concept of brain tumour grading was introduced that forms the basis of modern-day neuro-oncology [1]. Prior to this pioneering work, attempts at distinguishing types of brain tumours were made by Rudolf Virchow and Camillo Golgi. During this time, virtually all brain tumours were called gliomas, but low-grade (now grades 1 and 2) were seen as a distinct entity compared to high-grade (now grades 3 and 4) gliomas [2]. For 3 years Bailey examined and classified the pathological material of 414 glioma cases from Cushing's series classifying these tumours into 13 categories. A year later, in 1927, the glioma classification was simplified into 10 groups, in which tumour type was linked to the length of survival. Among others, oligodendroglioma, ependymoma, and astrocytoma were already separate groups [1]. Since 1979 the World Health Organization (WHO) has published the classification of tumours of the nervous system [3]. Until 2016, classifications relied primarily on histology, comparable to almost a century ago. However, more recent studies reported that molecular classification allowed for an improved prognostic classification with better treatment selection [4]. Gliomas with isocitrate dehydrogenase (IDH) mutations and 1p/19q codeletion respond better to radiotherapy and chemotherapy with a longer overall survival time compared to IDH-wildtype and non-codeleted tumours, respectively [5, 6]. Therefore, in the 2016 classification of central nervous system (CNS) tumours, histologic and molecular characteristics were combined to define tumour entities.

Brain tumours can either originate in the brain, referred to as a primary brain tumour or metastasise to the brain as a result of a systemic cancer (mainly from non-small-cell lung cancer, breast cancer, and melanoma) and is then called a secondary brain tumour, or brain metastasis [7]. More than 100 different CNS tumours are included in the WHO 2016 classification. The primary CNS tumours are graded, ranging from WHO grade 1–4. Grade 1 CNS tumours are benign and commonly curable with complete surgical resection. Typical examples of grade 1 CNS tumours include meningothelial meningiomas, pilocytic astrocytomas, and subependymomas. Grade 2–4 CNS tumours are malignant and are, besides surgical resection, commonly treated with radiotherapy and/or chemotherapy. Typical examples of grade 2–4 CNS tumours include oligodendrogliomas, anaplastic astrocytomas IDH-mutant, and glioblastomas, respectively [8]. The latter comprise 57% of all gliomas with an annual incidence of ~3 per 100.000 persons, while gliomas comprise 26% of all primary brain tumours [9]. In contrast, brain metastases have an annual incidence of ~10 per 100.000 persons according to population-based studies, but the true incidence is probably significantly higher according to autopsy studies [7]. The median overall survival of patients with 1–3 brain metastases is 10 months after stereotactic radiosurgery

treatment [10]. Median overall survival of glioblastoma patients is only slightly better, 15 months after surgical resection, radiotherapy, and chemotherapy [11]. The prognosis of grade 2 IDH-mutant gliomas treated with radiotherapy and chemotherapy is more optimistic with a median overall survival of 13 years [12]. With regard to gliomas, grade 1 tumours primarily occur in children, while grade 2–4 tend to occur in adults [13]. Typically, outcomes in the field of neuro-oncology were focused on progression-free and overall survival, but health-related quality of life (HRQoL) as outcome has received increased attention in the past decades and is usually included as a secondary outcome in large clinical trials. In this chapter, we focus on the level of HRQoL in adult patients with grade 2–4 gliomas of astrocytic or oligodendroglial origin.

This chapter enables readers to gain more knowledge about the following: (a) The assessment of HRQoL in glioma patients. (b) The effects of determinants on HRQoL such as surgery, radiotherapy, chemotherapy, mood, and epilepsy. (c) HRQoL as prognostic factor for survival. (d) Long-term survivorship. (e) Caregivers' HRQoL. (f) HRQoL in the end-of-life phase. Each section is preceded by a small summary of the findings of that specific section.

23.2 Assessment of HRQoL in Glioma Patients

HRQoL has become an important outcome in glioma research, typically assessed with cancer-specific questionnaires in combination with a brain tumour-specific module.

HRQoL outcomes are evaluated in glioma patients for mainly two reasons. In clinical trials, HRQoL as a secondary outcome contributes to determine the net clinical benefit of a treatment strategy together with the primary outcome (e.g. overall survival). In clinical practice, regularly assessing HRQoL during the course of the disease provides the treating physician with valuable information about the patients' functioning and symptoms, thereby aiding in personalised medicine [14]. The most frequently used HRQoL questionnaires in the glioma population are the European Organization for Research and Treatment of Cancer (EORTC) Quality of Life Questionnaire (QLQ-C30) in combination with the brain cancer module (QLQ-BN20) and the in the United States of America developed Functional Assessment of Cancer Therapy-General (FACT-G) in combination with the FACT-Brain Cancer Subscale (FACT-BrCS). Both the EORTC and FACT questionnaires are validated in brain tumour patients [15] (see also Chaps. 5 and 6, this volume).

Table 23.1 Content of the EORTC QLQ-C30 version 3.0

	Number of items	Range item scores	Scale scores
Global health status/QoL	2	1–7	0–100
Functional scales			
Physical	5	1–4	0–100
Role	2	1–4	0–100
Emotional	4	1–4	0–100
Cognitive	2	1–4	0–100
Social	2	1–4	0–100
Symptom scales			
Fatigue	3	1–4	0–100
Nausea and vomiting	2	1–4	0–100
Pain	2	1–4	0–100
Dyspnoea	1	1–4	0–100
Insomnia	1	1–4	0–100
Appetite loss	1	1–4	0–100
Constipation	1	1–4	0–100
Diarrhoea	1	1–4	0–100
Financial difficulties	1	1–4	0–100

The EORTC QLQ-C30 consists of 30 items and the EORTC QLQ-BN20 of 20 items (Tables 23.1 and 23.2). Scores on the EORTC items are transformed to a linear scale ranging from 0 to 100 and sum scores can be computed for multi-item scales. With regard to the functioning scales, a higher score means better functioning. With regard to the symptom scales, a higher score means worse symptomatology. The FACT-G consists of 27 items and the FACT-BrCS of 23 items (Table 23.3). The two combined form the FACT-Brain (FACT-Br), consisting of 50 items, of which the scores can ultimately be added up

Table 23.2 Content of the EORTC QLQ-BN20

	Number of items	Range item scores	Scale scores
Future uncertainty	4	1–4	0–100
Neurological deficit scales			
Motor dysfunction	3	1–4	0–100
Communication deficit	3	1–4	0–100
Visual disorder	3	1–4	0–100
Symptom scales			
Headaches	1	1–4	0–100
Seizures	1	1–4	0–100
Drowsiness	1	1–4	0–100
Hair loss	1	1–4	0–100
Itchy skin	1	1–4	0–100
Weakness of legs	1	1–4	0–100
Difficulty controlling bladder	1	1–4	0–100

Table 23.3 Content of the FACT-Br version 4.0

	Number of items	Range item scores	Scale scores
FACT-G subscales			
Physical well-being	7	0–4	0–28
Social well-being	7	0–4	0–28
Emotional well-being	6	0–4	0–24
Functional well-being	7	0–4	0–28
FACT-BrCS	23	0–4	0–92

reflecting a total HRQoL score (total score ranges from 0 to 200, with a higher score representing better HRQoL) [15].

Other questionnaires that also have been frequently used in past clinical trials, which will be discussed in this chapter, are explained briefly in this paragraph. The MD Anderson Symptom Inventory (MDASI) is a questionnaire developed to score both symptom severity (13 items) and its impact on daily functioning (6 items) in cancer patients. The MDASI-Brain Tumor (MDASI-BT) module also assesses symptom severity of nine symptoms specific to brain tumours. Scores range from 0 to 10 for each item, with higher scores indicating worse symptom severity and interference with daily functioning. Six underlying constructs are measured by the 22-item MDASI-BT, including affective, cognitive, focal neurological deficit, treatment-related symptoms, generalised symptoms, and gastrointestinal [16]. Another relatively often used generic HRQoL questionnaire in glioma patients is the 36-item Short Form (SF-36), including eight different domains (physical functioning, role limitations due to physical health, role limitations due to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health) and two summary scores, the physical and mental component summary scores. Domain and summary scores range from 0 to 100, with a higher score indicating a more favourable health status [17]. The Ferrans and Powers Quality of Life Index (FPQLI) was developed to measure QoL in terms of satisfaction with life and the importance with regard to various aspects of life and contains 66 items, with a range in scores of 1–6 for each item. The FPQLI gives a total QoL score including all items and scores on four domains: health/functioning, psychological/spiritual, social/economic, and family [18]. The Functional Living Index-Cancer (FLIC) contains 22 items and each item has a score range of 1–7. A total summary score is computed, with a higher score indicating better HRQoL [19]. For glioma patients, five domains can be distinguished as measured with the FLIC, including psychological well-being, role/sociability, inner experience of disease, isolation/sharing, and nausea [20]. The 31-item Quality of Life in Epilepsy Inventory (QOLIE-31) has been used a few times in brain tumour-related epilepsy research and consists of seven domains, including overall QoL, seizure worry, emotional well-being, energy/fatigue, cognitive functioning, medication effects, and social functioning. Scores for each scale range from 0 to 100, with a higher score indicating better HRQoL [21–24]. Many other HRQoL questionnaires have been used in the glioma population, but these questionnaires will not be described here [25].

Clinically meaningful difference (or minimally important difference) is defined as a difference in the score of the outcome of interest (e.g. HRQoL score) that is seen as important by either

the patient or its proxy and which would lead the patient or its treating physician consider a change in the patient's management. Determining what is a clinically meaningful difference is important for HRQoL data, because these scores are useful to patients, clinicians, and researchers, as these differences can be used for assessing the success of a treatment and establishing adequate sample sizes of future clinical trials [26]. Only the EORTC QLQ-C30 and EORTC QLQ-BN20 questionnaires have a clear definition for a clinically meaningful change on scales for glioma patients. A difference of ≥10 points on a scale was traditionally seen as a clinically meaningful difference for all scales in all cancers of the EORTC questionnaires, but cancer-specific minimally important differences are now being developed. In this chapter, if it is known whether a significant difference is also clinically meaningful, this will be indicated with an asterisk (*). The clinically meaningful difference was mentioned and interpreted in 42% (58/138) of longitudinal studies that evaluated HRQoL over time in glioma patients [27].

23.3 Effect of Sociodemographic Factors and Performance Status on HRQoL

Conflicting evidence exists about the impact of most sociodemographic factors on HRQoL scores.

In three studies, female sex has been related to a significantly lower global health status and lower total HRQoL score in glioma patients [28–30], but five studies found no significant differences between men and woman with regard to HRQoL [31–35]. Age and ethnicity did not seem to have an effect on HRQoL [28, 31, 32, 34, 36, 37]. In two studies, it was demonstrated that patients being single, widowed, or divorced had a significantly lower total HRQoL score and lower scores on all domains of the FPQLI questionnaire compared to those who were married or in a relationship [34, 37], but in three other studies marital status was not associated with HRQoL [20, 31, 32]. A lower level of education was found to be related to significantly lower functional well-being [33], global health status* [35], and total HRQoL score [32], but this effect was not apparent in three other studies [31, 34, 37]. Evidence seems somewhat less conflicting for performance status. Most often the Karnofsky Performance Status (KPS) is used to quantify a glioma patient's general well-being and activities of daily life, with a score ranging from 0 to 100. A higher score indicates less symptoms and a higher level of functioning [38]. The KPS is a clinician-observed outcome and therefore scored by a physician or nurse. It is therefore an inadequate surrogate for HRQoL, as this is typical a patient-reported outcome, reflecting the patients' perspective [39]. However, the KPS is valuable for other purposes, such as quickly assessing a patients functional status and is an important prognostic factor for overall survival [40]. A KPS score <70 is often used as cut-off to exclude patients from participation in trials. A low performance status has been related to a reduced mental and physical component summary score [41], global health status* [35], and total HRQoL score [31, 32], but this effect was not demonstrated in one other study [42].

23.4 Effect of the Tumour and Surgery on HRQoL

Surgical resection of the tumour seems to have a positive effect on HRQoL scores by a reduction of the tumour mass and accompanying symptoms, while tumour recurrence seems to have a negative effect on HRQoL scores. Tumour characteristics, such as location and tumour grade, show contradictory results regarding their impact on HRQoL.

Surgical resection of the tumour prolongs survival and may alleviate neurological symptoms. However, surgery might damage normal surrounding tissue, thereby inducing neurological deficits, including neurocognitive dysfunction and behavioural problems. HRQoL scores of newly diagnosed and histologically confirmed glioma patients were similar to those of newly diagnosed non-small-cell lung cancer patients

[41], but worse than healthy controls [41, 43, 44], HRQoL scores were significantly worse in patients who underwent biopsy compared to surgical resection. In addition, patients who underwent biopsy were less likely to show improvement in their HRQoL scores over time, whereas HRQoL scores of patients who had undergone gross total tumour resection did improve over time [45]. Of note, biopsy patients are considerably different from patients undergoing surgical resection, meaning the results are biased. Biopsy-only patients tend to have a lower performance status, more often a multifocal tumour, a larger tumour size, and the tumour is often localised in a surgically more difficult accessible region, because these factors preclude them from being able to undergo surgery [15]. Still, the findings from this study support the idea that early side effects of surgical resection seem (mostly) transient.

Despite aggressive treatments (surgery, radiotherapy, and systemic therapy), HRQoL seemed to improve during the disease trajectory, given patients do not have active disease [32]. Glioma patients showing tumour recurrence had even worse HRQoL scores compared to newly diagnosed glioma patients and compared to patients with localised cancer (i.e. confined to a certain part of the body, usually in the tissue or organ where the cancer originated), but HRQoL was similar to that of patients with metastatic cancer. Tumour recurrence in glioma patients was significantly more often accompanied with neurological symptoms, including motor dysfunction* and communication deficits*, than at time of diagnosis [46, 47].

The effect of tumour grade on HRQoL shows contradictory results. In a number of studies, no significant differences were found in HRQoL between patients with grade 3 and 4 glioma [32, 37, 47, 48], but in one study glioblastoma patients had worse scores on the role/sociability scale and total HRQoL score [20]. The worse HRQoL scores in glioblastoma patients were ascribed to the more aggressive nature of this tumour. Generally, it is thought that glioblastoma patients have shorter periods of stable HRQoL due to a shorter time to tumour progression and neurocognitive decline. Whether having a glioma in either the left or right hemisphere is related to worse HRQoL scores is controversial, as both the left and right hemispheres have been correlated with reduced HRQoL scores [39]. Also with regard to tumour location, there is no unambiguous relationship [49]. Finally, tumour volume did not seem to be related to HRQoL scores [34, 42, 50].

23.5 Effect of Radiotherapy on HRQoL

Radiotherapy does seem to induce transient negative effects on certain HRQoL scales on the short term, such as motor dysfunction and communication deficits. Most important long-term effects of radiotherapy are neurocognitive deficits in various domains, which have a negative effect on HRQoL.

Radiotherapy is part of standard treatment in most glioma patients aiming to improve local tumour control, preserve a patients' functioning, and increase overall survival. The timing, dosing, and scheduling of radiotherapy depend on the tumour and other prognostic factors [51]. Most of the time, patients will undergo a radiotherapy scheme of 3 or 6 weeks. Radiotherapy on the one hand may stabilise or improve HRQoL outcomes by delaying renewed tumour growth. In elderly newly diagnosed glioblastoma patients, radiotherapy was compared to supportive care only. Radiotherapy increased the overall survival, but it did not result in differences with regard to HRQoL (Table 23.4). In both treatment arms, physical functioning*, cognitive functioning*, social functioning*, and fatigue* significantly deteriorated over a period of 4.5 months. Thus, radiotherapy treatment had no additional negative effect on HRQoL [52]. In a clinical trial in patients with grade 3 glioma comparing radiotherapy alone with radiotherapy plus procarbazine, lomustine, and vincristine (PCV) chemotherapy, no negative effects of radiotherapy on HRQoL were found. Significant improvements from baseline in overall HRQoL* and social functioning* were seen in both the radio-

Table 23.4 Outcomes in major clinical trials in glioma patients

Study	N total	Glioma grade	Treatment arms	Median OS in months	Median PFS in months	HRQoL (on the prespecified scales)
Newly diagnosed						
Baumert et al. (2016) [54, 58]	477	2	RT vs. TMZ	–	46 vs. 39	Global health status at 3 months, communication deficit at 9 and 18 months, social functioning at 3 months, and motor dysfunction at 3 months were worse for RT
Cairncross et al. (2013) [5, 59]	291	3	RT vs. RT + PCV	56 vs. 55	20 vs. 31	No differences between treatment arms
Van den Bent et al. (2006) [44, 60]	368	3	RT vs. RT + PCV	31 vs. 40	13 vs. 23	Fatigue at 6 months,[a] physical functioning at 6 months,[a] and nausea and vomiting at 3 and 6 months were worse for RT + PCV
Wick et al. (2012) [55]	412 (>65 years)	3 and 4	RT vs. TMZ	10 vs. 9	5 vs. 3	Only communication deficits were worse at 3 months for RT[a]
Keime-Guibert et al. (2007) [52]	85 (≥70 years)	4	SC vs. SC + RT	17 vs. 29	5 vs. 15	No differences between treatment arms
Stupp et al. (2005) [11, 43]	573	4	RT vs. RT + TMZ	12 vs. 15	5 vs. 7	Only social functioning at 3 months worse for RT + TMZ[a]
Stupp et al. (2017) [61, 62]	695	4	RT + TMZ vs. RT + TMZ + TTF	16 vs. 21	4 vs. 7	Only itchy skin at 3, 6, and 9, but not 12 months worse for TMZ + TTF[a]
Malmström et al. (2012) [57]	342 (≥60 years)	4	TMZ vs. RT vs. HFRT	8 vs. 7 vs. 8	–	HRQoL scores on domains were generally better for TMZ,[a] but global health status equal between treatment arms
Chinot et al. (2014) [63]	921	4	RT + TMZ vs. RT + TMZ + BEV	17 vs. 17	6 vs. 11	No differences between treatment arms
Gilbert et al. (2014) [64]	637	4	RT + TMZ vs. RT + TMZ + BEV	16 vs. 16	7 vs. 11	Cognitive functioning, motor dysfunction, and communication deficits, and various symptom scales of the MDASI-BT were worse at 8 and 11 months
Herrlinger et al. (2016) [65]	182	4	RT + TMZ vs. RT + BEV + IRI	18 vs. 17	6 vs. 10	No differences between treatment arms
Herlinger et al. (2019) [66, 67]	141	4	RT + TMZ vs. RT + TMZ + CCNU	31 vs. 48	17 vs. 17	No differences between treatment arms
Recurrent/progressive						
Van den Bent et al. (2018) [68]	155	2 and 3	TMZ vs. TMZ + BEV	15 vs. 13	6 vs. 6	No differences between treatment arms

(continued)

Table 23.4 (continued)

Study	N total	Glioma grade	Treatment arms	Median OS in months	Median PFS in months	HRQoL (on the prespecified scales)
Brada et al. (2010) [69]	447	3 and 4, after RT	PCV vs. TMZ-5 vs. TMZ-21	7 vs. 9 vs. 7	4 vs. 5 vs. 4	Global health status worse at 3 months, but not 6 months for PCV and TMZ-21[a]
Stupp et al. (2012) [70]	237	4	Active control vs. TTF	6 vs. 7	2 vs. 2	Cognitive functioning, appetite loss, constipation, diarrhoea, fatigue, nausea and vomiting, and pain at 3 months all worse for active control[a]
Wick et al. (2010) [71]	266	4	ENZ vs. CCNU	7 vs. 7	2 vs. 2	No differences between treatment arms
Wick et al. (2017) [72]	437	4	CCNU vs. CCNU+BEV	9 vs. 9	2 vs. 4	Only social functioning at baseline and social functioning and global health status at 9 months worse for CCNU+BEV,[a] but not at 3 or 6 months
Lombardi et al. (2019) [73, 74]	119	4	CCNU vs. REG	6 vs. 7	2 vs. 2	Only appetite loss worse for REG

BEV bevacizumab, *CCNU* lomustine, *ENZ* enzastaurin, *HRQoL* health-related quality of life, *HFRT* hypofractionated radiotherapy, *IRI* irinotecan, *MDASI-BT* MD Anderson Symptom Inventory Brain Tumor, *N* number of patients, *OS* overall survival, *PCV* procarbazine, lomustine, and vincristine, *PFS* progression-free survival, *REG* regorafenib, *RT* radiotherapy, *SC* supportive care, *TMZ* temozolomide, *TMZ-5* temozolomide 5-day schedule, *TMZ-21* temozolomide 21-day schedule, *TTF* tumour-treating fields, *vs.* versus

[a]Significant and clinically meaningful

therapy and radiotherapy plus PCV group after 18 months of follow-up [44].

On the other hand, radiotherapy may have a negative effect on HRQoL, both on the short (e.g. fatigue) and long term (e.g. neurocognitive impairment). These long-term effects are most relevant for low-grade glioma patients as most high-grade glioma patients have died by the time these effects occur. Neurocognitive domains affected on the long term (mean of 12 years) in irradiated compared to radiotherapy-naïve grade 2 glioma patients, included attention, information processing speed, and executive functioning [53]. These neurocognitive deficits subsequently seemed to have an impact on HRQoL scores [41]. Short-term negative effects of radiotherapy have been demonstrated in various studies in glioma patients. Radiotherapy has been compared to temozolomide (an alkylating chemotherapeutic agent) in grade 2 glioma patients. Patients treated with radiotherapy showed mainly significantly worse scores on HRQoL scales, such as communication deficit and motor dysfunction, at the end of radiotherapy treatment. Hair loss* seemed to persist for a longer period, but eventually this improved over time as well. HRQoL scores at 36 months were on all scales comparable to baseline for patients treated with radiotherapy and temozolomide [54]. In a study by Wick et al. (2012), comparing radiotherapy with temozolomide in elderly grade 3 and 4 newly diagnosed glioma patients, significantly worse communication deficits* were found at 3 months follow-up for the radiotherapy group, but over time HRQoL scales remained stable [55]. Radiosurgery as an additive to radiotherapy and carmustine was compared to radiotherapy plus carmustine in another trial in newly diagnosed glioblastoma patients. At the end of radiotherapy, 42% of patients had shown deterioration in overall HRQoL score in the radiotherapy plus carmustine group and 49% in the radiosurgery additive

group, but this difference was not significant [56]. Malmström et al. (2012) found in a trial no difference between hypofractionated radiotherapy or conventional radiotherapy on HRQoL scores [57].

23.6 Effect of Chemotherapy on HRQoL

*Chemotherapy (*i.e. *temozolomide, PCV, and lomustine) in glioma patients seems to have a minor negative effect on HRQoL. Scores on HRQoL scales reflecting the typical adverse effects of chemotherapy (*e.g. *nausea and vomiting) tend to be temporarily worse during chemotherapy.*

In most glioma patients, radiotherapy is combined with chemotherapy as part of standard care. Temozolomide, a drug that has a good blood-brain barrier penetration and a favourable safety profile, is most commonly administered. The main toxicity concerning temozolomide is thrombocytopenia, which might require adjusting the dosage or early discontinuation of the prescribed number of cycles (in most cases 6–12 cycles) [51]. In 2005, Stupp et al. published the results of a major breakthrough in the field of neuro-oncology: the addition of temozolomide to radiotherapy had a significant survival benefit for newly diagnosed glioblastoma patients (Table 23.4) [11]. With regard to HRQoL, only social functioning* at 3 months was significantly worse for radiotherapy combined with temozolomide compared to radiotherapy alone [see research in context]. HRQoL scores on the various scales remained much the same for both treatment arms [43]. In a study comparing radiotherapy with temozolomide in grade 2 glioma patients, scores on HRQoL scales reflecting the typical adverse effects of chemotherapy (nausea and vomiting, appetite loss, and constipation) were significantly worse at 6, 9, and 12 months, corresponding with the end of the chemotherapy cycles. Adverse effects were transient as scores on these HRQoL scales improved at subsequent follow-up [54]. Two different schedules (a 5-day and 21-day) of temozolomide were compared with PCV chemotherapy in recurrent high-grade glioma patients. The 5-day temozolomide schedule group had a significantly better global health status* at 3 months, but this difference was only transient as it was no longer present at 6 months follow-up [69].

PCV is the most widely used combination of chemotherapeutic agents after temozolomide in mainly grade 2 and 3 glioma patients. Its efficacy and effect on survival and HRQoL has been studied in two large trials in newly diagnosed grade 3 glioma patients. In one trial, no differences between the two treatment arms (radiotherapy vs. radiotherapy plus PCV) were found concerning HRQoL scores until the last year of life, when scores deteriorated equally rapid in both groups [5, 59]. The other trial showed that the addition of PCV to radiotherapy resulted in nausea and vomiting, fatigue*, and physical functioning* at 6 months, but these adverse effects were only transient, as they were no longer apparent during subsequent follow-ups [44, 60].

Lomustine (an alkylating nitrosourea chemotherapeutic agent) has become the standard-of-care in recurrent glioblastoma [75]. It was compared to enzastaurin (a serine/threonine kinase inhibitor) in recurrent glioblastoma patients, and no differences in HRQoL scores were found between the two treatment arms. The 6-month clinically meaningful total HRQoL score deterioration rate was 18% for enzastaurin and 29% for lomustine [71]. The addition of lomustine to conventional treatment in newly diagnosed glioblastoma patients, that is, radiotherapy plus temozolomide, had no negative effect on HRQoL [66, 67].

23.7 Effect of Immunotherapy, Targeted Therapy, and Other Anti-Tumour Treatments on HRQoL

*Immunotherapy (*e.g. *bevacizumab), targeted therapy, and other anti-tumour treatments (*e.g. *tumour-treating fields) do not seem to have a substantial negative effect on HRQoL.*

Bevacizumab, an anti-VEGF (vascular endothelial growth factor) monoclonal antibody, has

been studied in grade 2–4 glioma patients, both in the newly diagnosed and tumour recurrence setting (Table 23.4). In newly diagnosed glioblastoma patients, the addition of bevacizumab to conventional treatment prolonged the deterioration-free survival time on all 26 HRQoL scales, which was explained by the prolonged progression-free survival time with this treatment as the time to deterioration (excluding progression as an event) in HRQoL was not prolonged. This means that the addition of bevacizumab did not have a negative, nor positive, impact on the patients' HRQoL [63]. The study of Gilbert et al. (2014) showed comparable results with regard to overall and progression-free survival, but different results with regard to HRQoL. Bevacizumab was reported to have a significant negative effect on multiple HRQoL scales [64]. No significant differences in HRQoL scores were detected between conventional treatment versus radiotherapy plus bevacizumab plus irinotecan (a chemotherapeutic agent) in newly diagnosed O^6-methylguanine-DNA methyltransferase non-methylated glioblastoma patients. Although in the experimental arm, scores deteriorated significantly over time for social functioning* and motor dysfunction [65]. In progressive glioblastoma patients, the addition of bevacizumab to lomustine had a significant negative effect on social functioning* and global health status* at 9 months (last HRQoL follow-up included in the analysis), but not at 3 or 6 months, while it did not confer an overall survival advantage over lomustine alone [72]. In recurrent grade 2 and 3 glioma patients, the addition of bevacizumab to temozolomide had no negative effect on HRQoL scores [68].

In a recently published phase 2 trial in recurrent glioblastoma patients, regorafenib (a multikinase inhibitor) showed a significantly improved overall survival compared to lomustine, at the expense of significantly worse appetite loss scores [73, 74]. In a phase 2 trial of cilengitide (an integrin-targeting arginine-glycine-aspartic acid peptide) in recurrent glioblastoma, this agent showed no negative effect on HRQoL scores during subsequent follow-ups compared with baseline [76].

Finally, the addition of tumour-treating fields (an antimitotic treatment modality that is thought to exhibit its effect by alternating electric fields in low intensity and intermediate frequency delivered through noninvasive transducer arrays, which are placed around the anatomic region of the tumour locoregionally) showed to significantly increase overall survival in newly diagnosed glioblastoma patients compared to conventional treatment with radiochemotherapy, while only itchy skin* was significantly worse with tumour-treating fields [61, 62]. When compared with an active chemotherapy control group in recurrent glioblastoma patients, the tumour-treating fields group had significantly better scores on cognitive functioning*, emotional functioning, role functioning, appetite loss*, constipation*, diarrhoea*, fatigue*, pain*, nausea and vomiting*, while physical functioning was worse at 3 months (no further follow-up) [70].

23.8 Effect of Neurocognitive Impairment and Its Treatment on HRQoL

Neurocognitive impairment is associated with decreased HRQoL scores in certain scales in both low-grade and high-grade glioma patients.

Neurocognitive functions are so-called higher order brain functions, which are involved in acquiring and process information. Neurocognitive domains include, among others, memory, executive functioning, and attention. In contrast, basic functions of the central nervous system include sensory, motor, and autonomic functions. Neurocognitive functioning can be assessed by either subjective questionnaires or objective cognitive tests. Subjective cognitive functioning measures self-reported cognitive complaints; the six-item Medical Outcomes Study cognitive-functioning scale is a frequently used questionnaire to assess these cognitive complaints in glioma patients. However, glioma patients might overestimate (e.g. due to a frontal tumour interfering with their judging abilities) or underestimate (e.g. due to a depressed mood) their cognitive abilities. Therefore, neurocognitive functioning

should always be assessed objectively as well, by using cognitive tests such as the Rey auditory verbal learning test, the trail-making test, or the Stroop colour-word test, depending on the domains that are considered relevant [77]. The Mini-Mental State Examination, an instrument developed to screen patients' neurocognitive impairments, is less suitable for glioma patients. Indeed, the instrument is less sensitive in detecting neurocognitive impairment and particularly in detecting (subtle) neurocognitive alterations over time in brain tumour patients [78, 79].

Neurocognitive dysfunction interferes with the patient's ability to maintain activities of daily living [80]. Up to 90% of brain tumour patients exhibit an impairment in at least one neurocognitive domain at diagnosis, when assessed with objective cognitive tests [81]. Neurocognitive deficits can be caused in brain tumour patients by a wide array of causes, including the tumour itself, surgical resection, radiotherapy, chemotherapy, epilepsy, antiepileptic drugs, corticosteroids, or by mood disorders. Most likely a combination of all these factors contribute to the neurocognitive impairment in glioma patients [77]. Neurocognitive impairment is associated with significantly worse HRQoL scores in both low-grade and high-grade glioma patients [41, 82]. Significantly worse performance with ~1 standard deviation below the normative mean on all neurocognitive domains assessed in general (executive functioning, [information] processing speed, working memory, and attention), except verbal memory, was associated with significantly worse physical and mental health component summary scores, motor dysfunction, more seizures, and future uncertainty. Other disease-specific symptoms such as headache, drowsiness, communication, and visual deficits were as well associated with neurocognitive impairment on several domains [82]. A lower information processing speed correlated with decreased emotional well-being, while worse self-reported cognitive functioning correlated with both a decreased emotional well-being and social functioning [41].

Given this close relationship between neurocognitive functioning and HRQoL, potential treatments to improve neurocognitive functioning in brain tumour patients have been evaluated, which may subsequently have an impact on HRQoL. In a phase 3 randomised controlled trial (RCT) comparing donepezil (an acetylcholinesterase inhibitor) with placebo (total n = 198), treatment with donepezil resulted in modest improvements of several neurocognitive domains at 24 weeks, and the effect was greatest among brain tumour patients (mainly gliomas) with more severe pretreatment neurocognitive deficits [83]. A larger positive effect of donepezil was seen on the HRQoL FACT-Br subscales emotional and social well-being in patients reporting more neurocognitive/brain-related symptoms at baseline. However, these improvements in HRQoL were only seen at 12, but not at 24 weeks [84]. Although not in glioma patients, memantine has been studied in a large RCT (total n = 508) in patients with brain metastases as prophylactic treatment before receiving whole-brain radiotherapy to preserve neurocognitive functioning. Overall, patients receiving memantine had a delayed time to neurocognitive decline compared to placebo, especially in memory, executive functioning, and information processing speed, domains that are considered most relevant for brain tumour patients [85]. Given these results, memantine seems a promising agent, but whether it is of additive value for glioma patients as well with regard to neurocognitive functioning and HRQoL remains to be determined.

Not only pharmacological treatments have been studied to improve or delay neurocognitive impairment, but also psychological treatments. A total of 140 glioma patients with neurocognitive deficits were randomised to an intervention (six weekly 2-h sessions of cognitive rehabilitation) or waiting list control group. After 6 months of follow-up, the intervention group performed significantly better on attention and verbal memory than the control group. However, no differences were found with regard to HRQoL domains [86]. Other pilot studies on psychological treatment have shown to improve neurocognitive functioning in glioma patients, but the impact on HRQoL was not assessed [87].

23.9 Effect of Psychostimulants and Corticosteroids on HRQoL

Psychostimulants do not seem to improve scores of HRQoL scales, and the effect of dexamethasone on HRQoL is still unknown.

Psychostimulants, such as methylphenidate and modafinil, have been found to improve fatigue and enhance neurocognitive functioning in various study populations [88–98]. Modafinil was compared with placebo in an RCT ($n = 37$) in glioma patients, it did indeed show an improvement in fatigue, neurocognitive functioning, and HRQoL scores, but it did not exceed the effects of placebo [99]. Two other RCTs, comparing prophylactic armadofinil versus placebo (total $n = 81$) and prophylactic methylphenidate versus placebo (total $n = 68$) in glioma patients undergoing radiotherapy, did not show differences between the two treatment arms after 8 weeks of treatment in neurocognitive functioning, fatigue, or HRQoL scores [100, 101]. Comparable to the other psychostimulants, fatigue and other HRQoL scales in patients receiving dextroamphetamine was similar to patients receiving placebo (total $n = 46$) [102].

Dexamethasone, a corticosteroid, has been used in the treatment of glioma patients for decades to effectively reduce tumour-associated oedema and improve the clinical condition and (neurological) symptoms of the patient [103]. Despite its abundant use, its effect on HRQoL in glioma patients has not been extensively studied. Hypothetically, the relief of symptoms and improving the clinical condition of glioma patients could result in improved scores on HRQoL scales. In a study of Klein et al. (2001), corticosteroid use was associated with better recognition memory in newly diagnosed high-grade glioma patients, but it was associated with lower physical component summary scores [41]. Whether corticosteroid use leads to worse physical functioning or if patients with worse physical functioning use corticosteroids cannot be concluded from this study, but the latter seems more plausible.

23.10 Effect of Epilepsy and Antiepileptic Drugs on HRQoL

Uncontrolled seizures are generally related to worse HRQoL, and antiepileptic drug (AED) treatment in glioma patients does not seem to have a negative impact on the level of HRQoL of patients.

Seizures are a frequently occurring symptom in glioma patients, and the incidence is inversely related with the tumour grade, meaning seizure incidence ranges in diffuse gliomas from ~25% in grade 4 glioblastoma IDH-wildtype to ~75% in grade 2 diffuse astrocytoma IDH-mutant and oligodendroglioma IDH-mutant 1p/19q codeleted patients [104]. Surgery, radiotherapy, and chemotherapy all seem to have a beneficial effect on seizure control in glioma patients [105, 106]. Standard-of-care is the start of AED treatment as soon as the first seizure has occurred [107]. Compared to healthy controls, patients with low-grade gliomas ($n = 195$) had significantly lower levels of HRQoL, which was similar to the HRQoL scores of non-brain tumour-related epilepsy patients. Uncontrolled seizures instead of AED use had the most negative effect on HRQoL. Patients with uncontrolled seizures had significantly worse physical and mental health component summary scores than seizure-free patients [108]. High-quality comparative effectiveness AED studies in glioma patients are currently lacking, but nowadays levetiracetam is one of the most commonly prescribed first-line AED [109, 110]. Levetiracetam has several advantages, including a lack of hepatic metabolism and no known pharmacological interactions. Two small studies ($n = 18$ and $n = 29$) in mainly glioma patients showed monotherapy levetiracetam resulted in a 6-month and 12-month seizure freedom of 89% and 72%, respectively. HRQoL scores remained stable as compared to baseline as measured with the EORTC QLQ-C30 or even significantly improved on the scale's medication effects, seizure worry, energy/fatigue, and social functioning as measured with the QOLIE-31 [21, 24]. In another study, pregabalin was prescribed as AED add-on in 25 brain tumour patients,

mostly glioma. The 6-month seizure freedom was 36% and again HRQoL scores remained stable from the start of treatment up to 6 months (EORTC QLQ-C30) or significantly improved on the seizure worry scale (QOLIE-31) [22]. In recent years, lacosamide has received increased attention in physicians treating brain tumour-related epilepsy. In a prospective multicentre observational study (n = 93), lacosamide was prescribed as AED add-on and resulted in a 6-month seizure freedom of 35%, while HRQoL scores remained stable over 6 months' time [111]. Comparable results were reported in another smaller study (n = 25) evaluating lacosamide [112]. Cytochrome P450 (CYP450) enzyme-inducing AEDs, such as carbamazepine, phenytoin, and to a lesser extent oxcarbazepine, are generally discouraged in glioma patients due to the potential interaction with certain chemotherapeutic drugs [113]. Oxcarbazepine monotherapy resulted in a 12-month seizure freedom of 40% in glioma patients with epilepsy, while HRQoL scores remained stable during these 12 months [23].

23.11 Effect of Depression and Anxiety Disorder and Their Treatment on HRQoL

Both depression and anxiety are closely associated with a reduced total HRQoL score in glioma patients. The efficacy of pharmacological treatment of depression and anxiety in glioma patients and its effect on HRQoL is yet unknown.

Psychiatric symptoms are common in glioma patients, with a prevalence of self-reported moderate anxiety and depression of ~30% and ~15%, respectively [114]. Especially female patients, patients with severe functional impairment, a past history of a mood disorder, and a lower educational level seem to be at higher risk to become anxious or depressed [115, 116]. With disease progression, both functional status and levels of anxiety worsen in glioma patients [117, 118]. About 40% of glioma patients are prescribed anxiolytics during their disease trajectory and about 17% antidepressants [119]. Using selective serotonin reuptake inhibitors did not have a negative effect on survival or experiencing severe toxicities in glioblastoma patients [120]. However, currently there are no high-quality studies on the efficacy of anxiolytics or antidepressants in glioma patients [121]. Such studies are warranted, because depression is associated with a shorter overall survival [122], while both depression and anxiety are closely associated with a reduced total HRQoL score in glioma patients [31].

International guidelines suggest that patients with a chronic physical condition, including glioma patients, and a depression should be treated with a combination of pharmacological and psychological treatment [123] (see also Chap. 20, this volume). Boele et al. (2018) conducted a nationwide RCT in glioma patients with depressive symptoms in which patients received a 5-week online course based on problem-solving therapy, which is a less intense variant of cognitive behavioural therapy, or were placed on a waiting list. The study (total n = 122) showed no evidence for the effectiveness of an internet-based guided self-help intervention for depression, or on the physical or mental health component summary scores [124]. The Making Sense of Brain Tumour programme, a home-based intervention including techniques from cognitive behavioural therapy, acceptance and commitment therapy, and interpersonal therapy, has proven more effective. In an RCT including 50 patients with the majority diagnosed with a glioma, those patients following 10 sessions of the programme had significantly lower levels of depression and higher levels of existential well-being and total HRQoL score than the waiting list group, but not lower levels of anxiety [125].

23.12 HRQoL as Predictor of Survival

HRQoL as a prognostic factor for overall or progression-free survival is of limited clinical utility.

In glioma patients, the factors, namely, age, performance status, extent of resection, adjuvant

treatment, tumour histology and molecular parameters, tumour diameter, and neurological deficits have all been proven to be important prognostic factors for overall survival in glioma patients [118, 126, 127] (see also Chap. 14, this volume). Studies in other cancer populations showed that HRQoL can be an independent prognostic factor for overall survival [128–130]. Besides the two main reasons for which HRQoL data is used in glioma patients, which have been previously discussed (i.e. determining the net clinical benefit in clinical trials and routine monitoring of the patient's functioning and well-being in clinical practice), HRQoL data could also be used as a stratification variable in clinical trials if it would be an independent prognostic factor that has additional value. Coomans et al. (2019) evaluated the added prognostic value of HRQoL data in a meta-analysis that was based on individual patient data from 15 RCTs, including 5217 patients. The final prognostic model included both clinical and HRQoL variables. Better cognitive and role functioning and less motor dysfunction of patients was related to increased overall survival. Less nausea and vomiting, more appetite loss, and better cognitive and role functioning were related to increased progression-free survival. However, the added prognostic value of HRQoL data beyond that of the established clinical factors for both overall survival and progression-free survival was small (1.1% and 0.7%, respectively) [14]. Given the small added value of including HRQoL data in a prognostic model, as well as the difficulty obtaining such information with patient-reported outcomes, the use of HRQoL data in clinical care for prognostic purposes or in clinical trials as a stratification factor is limited.

23.13 Long-Term Survivorship

Long-term survival seems to be particularly accompanied with deterioration of physical functioning over time.

Maintaining good levels of HRQoL is especially important in patients with long-term survivorship, as longer survival may be less meaningful for patients if this is at the expense of the patients' functioning and well-being. Especially patients with low-grade gliomas often experience long periods of stable disease, up to 15–20 years. HRQoL scores of low-grade glioma patients (n = 65) were compared with healthy controls at mid-term and long-term follow-up, ~6 and ~12 years since the time of diagnosis. Low-grade glioma patients had statistically significant lower scores on role limitations due to physical health and general health than healthy controls at long-term follow-up, but no other statistically significant differences were found between the two groups at mid-term or long-term follow-up. In low-grade glioma patients, only physical functioning significantly deteriorated over time, but no other statistically significant differences on HRQoL domains were detected [131]. Whether the low-grade glioma was located in an eloquent (i.e. involvement of sensorimotor regions, language cortices, basal ganglia, and/or larger white matter tracts) or non-eloquent brain region has no effect on HRQoL scores in the long term [132]. One study compared HRQoL scores of anaplastic oligodendroglioma and oligoastrocytoma patients (n = 32) with healthy controls as well as with patients' own HRQoL scores 2.5 years after initial treatment. Median overall survival of these patients was ~12 years since diagnosis. HRQoL scores of progression-free patients was significantly worse compared to healthy controls on the following domains: emotional*, social*, and cognitive functioning*, but their scores were similar to 2.5 years after initial treatment. Patients only significantly deteriorated in motor functioning over time. The addition of procarbazine, lomustine, and vincristine (PCV) to radiotherapy had no long-term negative effect on HRQoL compared to treatment with only radiotherapy, but the sample size was rather small [133]. When comparing high-grade glioma short-term (overall survival <1 year) with long-term survivors (overall survival >2 years), it appeared that scores on the general health domain of the short-term survivors deteriorated over 4 months while the long-term survivors improved at 16 months follow-up on pain, role limitations due to physical health, social, and physical functioning. Patients in the

long-term survivor group with tumour recurrence were reported to have significantly worse physical functioning, general health, and emotional well-being at 16 months follow-up compared to patients without recurrence [134]. Important to note with regard to long-term survivorship studies is the bias that patients with better health status are more likely to participate and remain in a study, potentially leading to an overestimation of HRQoL results on the long term [135].

23.14 HRQoL of the Caregivers

The level of HRQoL of caregivers of glioma patients is negatively affected during the entire disease course. Caregivers might benefit from cognitive behavioural therapy to cope with the high demands of taking care for a glioma patient.

Being diagnosed with a glioma may not only affect the patient's HRQoL, but it may also have its effect on the relative's HRQoL [136, 137]. Most often glioma patients have a partner who becomes the primary informal caregiver. While patients scored significantly worse on the physical component summary score compared to their informal caregivers in the early phase of the disease, informal caregivers scored significantly worse on the mental component summary score. Informal caregivers of patients with poor functional status reported higher levels of anxiety symptoms, and informal caregivers who had lower physical component summary scores were at increased risk of lower mental component summary scores [137]. Later in the disease phase, when patients were on chemotherapy, informal caregivers were highly burdened. About half reported to be anxious, another half to be sad, and they were significantly more often distressed than patients (55% of the informal caregivers vs. 47% of the patients). Informal caregivers reported a mean overall HRQoL score of 4.4 [138], while in the end-of-life phase this was 3.0 (based on one EORTC QLQ-C30 question, Likert scale 1–7, with 1 = extremely poor and 7 = very good) [139]. Of the informal caregivers, 28% and 14% reported moderate and poor levels of HRQoL, respectively [138]. Almost all informal caregivers (90%) reported sadness in the end-of-life phase, while 69% reported fear, 60% burn-out, 54% less interest in others, 29% felt incompletely prepared for their tasks, and 29% suffered from financial difficulties, the latter being significantly associated with a reduced overall HRQoL in the end-of-life phase in informal caregivers [139]. As mentioned above, almost a third of informal caregivers reported inadequate perceived caregiver mastery in the end-of-life phase [139], meaning they did not feel competent to successfully perform the activities related to providing care. Boele et al. (2013) conducted an RCT in which the intervention group had six 1-hour individual sessions with a psychologist, while the control group received care as usual. During these sessions, psychoeducation was given to informal caregivers, as well as cognitive behavioural therapy to increase the ability of caregivers to be able to cope with the demands of caring for a glioma patient. Feelings of caregiver mastery (i.e. the caregivers' level of self-efficacy to provide adequate care) increased over time in the intervention group, while the scores on the HRQoL scale emotional well-being remained stable. In the control group, however, feelings of caregiver mastery significantly worsened over time, which was true as well for the mental component summary score [140]. Psychological intervention therefore seems a helpful tool in supporting informal caregivers during this mentally heavily demanding period in their lives.

23.15 HRQoL in the End-of-Life Phase

In the end-of-life phase, patients' HRQoL scores are generally low and continue to decline as death approaches.

Despite the lack of consensus on the definition, the end-of-life phase in glioma patients is generally confined to the last 3 months of life. In this phase, anti-tumour treatment is no longer a valuable option, as the patient's condition declines and a shift in treatment goals occurs. Prolonging survival is no longer the primary aim, but reducing symptom burden and maintaining a

satisfactory level of HRQoL become the most important treatment goals [141]. Prevalence of disease-specific and general end-of-life symptoms in glioma patients vary considerably between studies, but common disease-specific symptoms include impaired consciousness (44–93%), delirium (15–85%), seizures (6–56%), dysphasia (39–48%), motor deficits (41–42%), dysphagia (8–85%), visual disturbances (22%), cognitive deficits (33–45%), and headache (33–62%). Common general end-of-life symptoms in glioma patients include fatigue (25–67%), incontinence (23–40%), bodily pain (10–25%), dyspnoea (12–24%), anxiety (9–18%), and depression (8–12%) [142, 143]. Glioma patients experiencing a high symptom frequency in the week before death reported a lower quality of care than patients experiencing a low symptom frequency [144]. Although the majority of glioma patients who died at home, died peacefully with a progressive loss of consciousness and their symptoms adequately controlled, still a non-peaceful death was reported in 13–18% of patients, mainly due to the presence of delirium or behavioural disturbances [145, 146]. Most glioma patients prefer to die at home, irrespective of the country of origin, but often this is not the actual place of death. In the Netherlands dying at home was most common (60% of patients) compared to 37% and 29% in Austria and Scotland, respectively. In Scotland, most patients died in a hospice (41%) and in Austria in a hospital (41%) [147].

Measuring the level of HRQoL of patients in the end-of-life phase is difficult, especially in glioma patients. In the end-of-life phase, glioma patients often have a poor health status, are neurocognitively impaired, and have a gradual reduction in consciousness, making it difficult to (near-)impossible to complete questionnaires [148]. Neurocognitive deficits appear to be the most important determinant for impaired medical decision-making capacity (i.e. treatment- and research-related decisions) in brain tumour patients, which have been reported to be present in 25–66% of brain tumour patients, with higher percentages in the end-of-life phase. In the situation where patients are not able to provide self-consent, surrogate consent by proxies (i.e. formal and informal caregivers) is an important alternative [149]. Acknowledging the difficulties discussed above, studies with a retrospective design relying on proxies for measuring the level of patient's HRQoL in the end-of-life phase are universally accepted [150]. Sizoo et al. (2014) developed a proxy-reported questionnaire to report on the level of HRQoL in high-grade glioma patients in the end-of-life phase. Besides domains which are covered in HRQoL questionnaires such as the EORTC QLQ-C30 and QLQ-BN20, spiritual well-being (i.e. acceptance of death and dying with dignity) was included as well. One study recruited 83 proxies of high-grade glioma patients who completed this study-specific HRQoL questionnaire, with a median of 27 months after the patient had died. Proxies reported a low overall quality of life of patients. Active participation in social activities and the family life of patients, according to proxies, was reported low too. However, received support from the patients' social environment and dying with dignity were reported to be high. As death approached, HRQoL scores of patients on various scales significantly deteriorated [148].

Advance care planning is the process in which patients and their proxies are involved in decision-making on future (palliative) care at an early stage in the disease trajectory. This allows the patient, their proxies, and the treating physician to examine all possible care options and thereby establish future goals for their care, including in the end-of-life phase. This is important due to the symptoms discussed previously, interfering with the patients' decision-making ability [151]. Indeed, communication deficits in patients were found to be a determinant for dying without dignity. Other determinants for dying without dignity included end-of-life decisions not being explained, not being satisfied with the physician in the last week, and transition between healthcare settings in the last month of life [152]. The expectation is that advance care planning is able to improve dying with dignity in glioma patients. Advance care planning has been shown to improve symptom scores, the total HRQoL score, and overall survival in metastatic lung cancer

patients in an RCT [153]. To what extent advance care planning would improve scores on HRQoL scales in glioma patients is unknown, but a disease-specific advance care planning programme has been developed for glioblastoma patients, and the impact of this programme on different outcomes, including HRQoL is currently being evaluated [151].

23.16 Conclusion

Given the overall survival of glioma patients is limited, HRQoL is an important secondary outcome in clinical trials in glioma patients, aiding in evaluating the most appropriate treatment for patients. From these clinical trials, it can be concluded that anti-tumour treatments mostly have a transient negative effect on HRQoL. The negative effect of anti-tumour treatments on HRQoL vary by treatment, but differences between treatments are not substantial. Besides evaluating the impact of anti-tumour treatment on HRQoL, a substantial number of studies have evaluated the effect of other determinants (e.g. sociodemographic factors and performance status) on HRQoL in glioma patients in the past decades. There is sometimes conflicting evidence among these studies that are mostly observational. However, it seems that symptoms such as epileptic seizures and neurocognitive impairment have a negative effect on HRQoL scores, but (non-) pharmacological treatment of these symptoms may stabilise or improve HRQoL scores.

23.17 Questions that Can Be Used for Learning/Testing

1. In general, what is the HRQoL trajectory in glioma patients during the course of the disease?
2. What were the main findings of the Stupp et al. (2005) trial?
3. What are the pros and cons of assessing patients' HRQoL in the end-of-life phase, prospectively in patients versus retrospectively by proxies?

23.18 A Topic for Discussion that Can Be Used for Teaching

1. Should maintaining optimal HRQoL versus prolonging overall survival be weighted differently in low-grade (grade 2) versus high-grade (grade 3 and 4) glioma patients? Clarify your answer.
2. When conducting a study in glioma patients in which HRQoL is included as (secondary) endpoint, how should this ideally be measured, analysed, interpreted, and reported?
3. Which research question with respect to HRQoL in glioma patients has most priority to date?

23.19 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

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23.20 Research in Context

Possibly the most influential paper in neuro-oncology in the past few decades, with >16.000 citations (as of April 2021, source: Google Scholar), is the manuscript by Stupp et al. (2005) in *The New England Journal of Medicine*. Since the 1980s, new drugs have been tested to improve overall survival in glioblastoma patients, but until 2005 no drug showed encouraging results. Temozolomide was the first drug that substantially increased overall survival in a well-designed RCT with an adequate control group. Since then, temozolomide is the mainstay in the treatment arsenal of neuro-oncologists. In the Stupp trial, patients receiving radiotherapy alone were compared with patients receiving radiotherapy plus temozolomide, which was given concomitantly during the radiotherapy and in an adjuvant phase after the radiotherapy in newly diagnosed, histologically confirmed glioblastoma patients. A total of $n = 573$ patients were included. The median survival was significantly longer in the radiotherapy plus temozolomide group (14.6 vs. 12.1 months) as well as the 2-year survival rate (26.5% vs. 10.4%). Haematologic grade 3 or 4 toxicity was observed in 7% of radiotherapy plus temozolomide patients versus 0% of the patients in the radiotherapy-alone group [11]. Seven predefined HRQoL measures of the EORTC QLQ-C30 and BN-20 were assessed at baseline and at every 3 months during treatment until disease progression. After 3 months, the radiotherapy-only group scored significantly (and clinically meaningful) better on social functioning than the radiotherapy plus temozolomide group, but at subsequent follow-up, HRQoL was comparable between the two treatment groups. Meaning, the addition of temozolomide has a negligible and temporary negative effect on HRQoL [43].

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Colorectal Cancer and Quality of Life

24

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24.1 Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed cancer worldwide (second amongst women and third in men) and the fourth most prevalent cause of oncological deaths worldwide [1]. In 2018, there were 1.8 million new cases diagnosed worldwide, with the incidence steadily on the rise [2]. Most CRC develops from adenomatous polyps in the colon or rectum, approximately 25–30% CRC diagnoses originate in the rectum. Incidence increases with older age with 83% of cases arising in people who are 60 years or older. There is variation in prevalence according to geographical region with greater incidence amongst developed countries including Australia, New Zealand, those in Europe and North America [1], although with the increasing infiltration of westernised lifestyles into developing countries, the epidemiology is changing [3]. The most common risk factors include diet (high red and processed meat consumption), obesity, sedentary lifestyle, high alcohol intake, smoking, inflammatory bowel disease and hereditary predisposition. Variability in exposure to risk factors (environmental and dietary), availability and uptake of screening and genetic testing, surveillance programmes and accessibility to treatment and health care facilities are likely to account for geographical disparity in prevalence as well as survival outcomes.

People who have completed curative intent treatment for CRC represent one of the largest groups of "survivors" of cancer affecting both men and women with 5-year survival rates of 65% [2]. For the 20% and 22% of people diagnosed with early or localised CRC (Stage I/Dukes' A or Stage II/Dukes' B, respectively), 5-year relative survival rates reach 91% and 82%, respectively. This is, however, in contrast to the rate of 12% for those with Stage IV (Dukes' D) advanced or metastatic disease [4].

Surgery is the mainstay treatment in cases of early, localised tumours. For patients with low rectal malignancies, abdominal perineal resection is carried out resulting in loss of the anal sphincter. However, 80% of patients with rectal cancer undergo sphincter-saving surgery. An intestinal *stoma (opening into the colon known as ostomy)* is often required for patients with *rectal cancer* and sometimes for *colon cancer as a temporary measure*. In the UK, almost 50% of rectal cancer patients have a stoma at 18 months post-surgery [5]. Stomas might also be placed temporarily for prophylactic reasons prior to radiotherapy or post-surgery to mitigate the risk of leaks. Patients with stomas in the palliative setting, as well as those with inadequate post-operative healing or other complications post chemotherapy and/or radiotherapy, are unlikely to have a stoma reversal.

The rate of permanent stoma formation after rectal cancer surgery varies considerably (ranging between 9% and 50% in England) [6]. Surgery and stoma formation are associated with significant morbidity on top of the side effects

associated with other treatments such as chemoradiotherapy.

Some patients with rectal cancer who have locally advanced disease benefit from treatment delivered before surgery in the form of chemoradiotherapy or short-course radiotherapy. This neoadjuvant treatment is nowadays indicated in such cases, reducing the risk of local recurrence. In addition, post-surgical chemotherapy (adjuvant treatment) is often delivered to patients with colon or rectal cancer to reduce the risk of systemic recurrence. In advanced or metastatic cases (stage IV/Duke's Stage D) and where surgical resection or other local treatments are not indicated, chemotherapy is recommended. More recently, targeted therapy and immunotherapy have opened up other treatment options to improve symptom control and survival [7, 8].

At the point of diagnosis, a patient might be troubled by bowel function-related symptoms as well as fatigue, weakness and pain. Subsequently, the often lengthy and complex treatment, including major surgery with or without a stoma and possible radiotherapy and/or chemotherapy, is likely to have a negative impact on multiple dimensions of life. Treatment effects include physical symptoms, such as bowel, urinary and sexual dysfunction and effects on psychological and social functioning, otherwise known as health-related quality of life (QOL). Furthermore, these effects can persist over time with the end of treatment not necessarily paired with relief from QOL concerns. The experience of surviving cancer can often be as hard as the diagnosis itself.

With the increasing number of people living with and beyond CRC, the need to monitor and manage QOL issues from the point of diagnosis, throughout the treatment trajectory and beyond, is recognised as imperative. QOL is recognised as a critical endpoint in cancer clinical trials alongside the traditional measures of treatment response rates and disease-free and overall survival. Indeed, the Food and Drug Administration (FDA) acknowledge the importance of QOL for supporting labelling claims [9] and QOL features prominently within the National Institute for Clinical Excellence (NICE) Guidelines for CRC [10]. As a result, survivorship care programmes have become more commonplace with interventions developed to manage the acute and late effects of CRC and improve QOL [11].

In this chapter, we will provide an overview of the QOL issues experienced by people with CRC with a specific focus on those that are particularly unique to this patient group. We will address the predictors of poor QOL and the importance of monitoring and managing QOL. We will outline and appraise the questionnaires that have been developed specifically for CRC. Finally, we will describe interventions to modify QOL outcomes.

This chapter will enable readers to gain more knowledge about (a) QOL concerns of specific relevance and importance to patients with CRC; (b) risk factors for poor outcomes in terms of QOL; (c) tools available to assess QOL in patients with CRC; (d) interventions to help patients mitigate the impact of CRC on QOL.

24.2 QOL Concerns of People Living with and Beyond CRC

Pre-diagnosis, some patients experience physical symptoms such as change in bowel habits, rectal bleeding, abdominal pain, weight loss, fatigue and weakness, prompting clinical investigation (blood tests and colonoscopy). Other patients present as asymptomatic with their route to diagnosis originating from routine screening. At diagnosis, regardless of physical symptom presentation, psychologically, patients might also be experiencing elevated levels of distress related to the diagnostic procedures, the diagnosis itself, or anxiety surrounding the treatment and outcomes. In a prospective cohort study involving patients with CRC, QOL was low at diagnosis (pre-surgery) for almost 30% of the sample [12]. Thus, the direct consequences of CRC on QOL might be felt early in the disease trajectory before treatment begins. In addition, each treatment has its own side-effect profile and potential consequences for QOL which are likely to be experienced beyond the end of treatment.

24.2.1 Bowel Function Problems

Given the location of the tumour and the nature of the resection and reconstruction surgery, bowel function problems are commonplace and change in bowel habits is reported by up to 90% of patients [13]. Even with sphincter preservation surgery, structural and nerve damage can lead to bowel dysfunction. Surgical resection, particularly in the case of low anterior resection, can lead to increased frequency and urgency of bowel movements due to smaller capacity of the rectum, lack of control resulting in faecal incontinence, sensation of incomplete evacuation (tenesmus), nocturnal bowel movements, constipation, abdominal pain and increased flatulence. These symptoms are also known collectively as low anterior resection syndrome (LARS), and in Dulska et al.'s review of 89 studies, 76% of patients were reported to experience LARS [14]. While for many patients bowel problems improve over time, there are reports of over 70% of patients experiencing problems longer than 1-year post-surgery [13].

Bowel problems impact on QOL not just in terms of physical discomfort but also psychologically and socially in terms of anxiety surrounding bowel movements, access to toilet facilities, embarrassment, body image concerns and social functioning due to avoidance of leaving the home and engaging in social activities often leading to a feeling of isolation. In a study of rectal cancer patients, faecal incontinence and urgency post-resection were negatively associated with social functioning, while urgency was also associated with poorer mental health and general health perception [13].

24.2.2 Stoma-Related Problems

Complications arising from ostomy surgery affect 21–70% of patients. Problems, often long-lasting, related to living with a stoma can be far reaching to include not only bowel function issues, flatulence and constipation but also urinary and sexual problems, depression, body image concerns, fatigue, dietary and lifestyle adjustments and embarrassment [15]. These problems are reflected in poorer QOL scores amongst patients who have a stoma compared with those who have had sphincter-preserving surgery [5]. Even patients who have had a stoma reversal have been shown to have poorer bowel control and more sexual problems compared with those who never needed a stoma.

24.2.3 Sexual Problems

The impact of CRC treatment on sexual function has been widely reported in the context of both acute and late effects [16, 17]. In a review of studies addressing sexual dysfunction following CRC, up to 88% of males were identified as experiencing problems compared with 50% of females. Problems relating to sexual functioning (erectile and ejaculatory problems for men and painful intercourse and vaginal dryness or atrophy for women), interest and enjoyment might be a consequence of pelvic damage following surgery or radiotherapy or cancer-related fatigue. In addition, sexual morbidity might have a more psychological basis and be intertwined with issues relating to body image, confidence and embarrassment, which, as mentioned above, can be magnified with the placement of a stoma.

24.2.4 Urinary Incontinence

Urinary function problems are a common adverse effect of CRC treatment, with pelvic and nerve injury resulting in long-term urinary retention and incontinence. Elevated risk levels are also experienced by people treated with neoadjuvant radiotherapy to the pelvic region [5, 18, 19]. Urinary incontinence was reported in one study as almost twice as prevalent in patients with rectal cancer compared with faecal incontinence, with numbers of diagnoses of urinary incontinence rising over a 5-year period [18].

24.2.5 QOL Issues Associated with Chemotherapy and Targeted Therapies

In addition to the toxicities related to radiotherapy and surgery, chemotherapy (5-fluorouracil, oxiplatin, capecitabine and irinotecan) can also negatively impact QOL of patients with CRC with its side effects often necessitating treatment modification or cessation [20–22]. Symptom burden associated with chemotherapy is also reported to increase in the days following treatment [23]. While each chemotherapy agent has its own unique toxicity profile, for example, oxiplatin-associated neuropathy, common chemotherapy side effects include lack of energy, neutropenia, alopecia, mucositis, diarrhoea, nausea and vomiting. Moreover, targeted therapies may be added to the treatment protocol as monotherapy or in combination with chemotherapy. Targeted therapies, of which bevacizumab, cetuximab and panitumumab were the first to receive approval for CRC, are more selective in their action compared with chemotherapy by inhibiting specific molecular pathways responsible for cancer growth and survival but they are not without their own, often unusual, side effects such as hypertension, gastrointestinal perforation and skin problems (rash, hand−foot syndrome). These are likely to be more prevalent amongst patients receiving targeted therapies in combination with chemotherapy [8].

24.2.6 Living Beyond CRC: QOL Issues

In a prospective 5-year study of people treated with curative intent for CRC, improvement in QOL was most notable 15 months following diagnosis. However, QOL levels did not return to baseline levels at all for around 30% of people [24] (for more information regarding this study, see the Research in Focus section). Many of the effects of CRC and its treatment noted above, such as fatigue, sleep difficulty, sensory neuropathy, bowel function problems, urinary incontinence and sexual dysfunction, persist well beyond the end of treatment [25, 26]. In a meta-synthesis of qualitative studies, the most common concern of CRC survivors, irrespective of stoma status, was bowel functioning including frequent and irregular bowel movements, loss of control over bowels and faecal incontinence [27].

The long-term and late effects might also be psychosocial in nature to include depression, anxiety, negative body image (particularly prominent for people who had a permanent stoma), reduced engagement in social activities and fear of recurrence, especially for people troubled by ongoing bowel function problems [25–27]. Where studies have reported similar [28] or indeed higher levels [29] of QOL amongst people post CRC diagnosis compared with non-cancer populations, issues relating to bowel function, such as diarrhoea, fatigue, depression levels, activity limitations and financial difficulties, separate the CRC cancer and non-cancer populations.

24.3 Risk Factors for Poor QOL

Several clinical and psychosocial factors have been identified as placing people at higher risk of poorer QOL outcomes following CRC. Tumour site and staging determine treatment protocol used and treatment duration, which in turn is inextricably linked to side-effect profile and intensity. In addition, individual factors such as socio-demographics and confidence to manage problems relating to CRC also play a role in QOL outcome.

24.3.1 Tumour Site

Evidence suggests that a diagnosis of rectal cancer is more detrimental to QOL in both the short and long term compared with colon cancer [24, 30] due to greater complexity of treatment regimens with higher likelihood of chemoradiotherapy (neoadjuvant and/or adjuvant) and abdominal perineal resection and an increased probability of stoma placement. When a tumour is higher up in the colon, there is also less risk of damage to nearby organs.

24.3.2 Treatment Type

Neoadjuvant radiotherapy has been associated with more late toxicity in terms of bowel, urinary and sexual function [5]. Treatment protocols using chemotherapy and radiotherapy have been associated with lower overall QOL scores as well as poorer role and social functioning [30]. Conversely, adjuvant therapy has been associated with lower odds of having worsened QOL at 5 years post-diagnosis [24].

24.3.3 Stoma Placement

Compared with people who have never had a stoma or who have undergone a stoma reversal, those who still have a stoma report significantly higher levels of sexual issues and worse overall QOL [5]. Stoma placement has also been found to be associated with problems relating to physical, role, emotional and social functioning [30]. A review of studies comparing patients with and without a stoma identified elevated social and psychological problems for those with a stoma, although bowel function problems were comparable across groups irrespective of stoma status [31].

24.3.4 Comorbidities

Living with health conditions alongside a diagnosis of CRC can add complexity to the disease and recovery process. A diagnosis of at least two other comorbidities has been shown to lead to worse QOL outcomes [24] particularly in people whose comorbidities limit their daily activities [32]. Depression and anxiety which limit daily activities have been identified as the comorbidities having the most significant impact on symptoms, functioning and QOL.

24.3.5 Sex

Studies comparing QOL outcome in men and women have produced inconsistent and often inconclusive findings. Women have been shown to have a higher risk of low physical functioning compared with men but better social and cognitive functioning following a diagnosis of CRC [30]. However, other studies have found the converse relationship with better psychosocial adjustment displayed by men [33]. As reported earlier, men have also reported more sexual problems following CRC compared with women [34].

24.3.6 Age

As with sex, the relationship between age and QOL outcome is also inconclusive, with some research suggesting people diagnosed at a younger age are more affected by the psychosocial impact of cancer [28, 35]. Other studies have identified older age as a risk factor for a lower QOL [30]. Younger people might have less well-developed coping mechanisms and less experience of serious health concerns such as cancer and might also be more likely to face concurrent challenges such as meeting financial commitments and supporting dependents. Older adults might experience higher physical burden of disease due to higher incidence of other health conditions and lower physical fitness. In addition, the way in which QOL is conceptualised might also vary according to age which might explain the more positive outlook of older adults [24].

24.3.7 Educational Status

Higher educational status has been found to be a protective factor in terms of global QOL and physical functioning [30]. This might be due to better access to health care, recovery packages, greater confidence to manage problems and ask for help and to know where to access support. Following a diagnosis of CRC, people with lower health literacy have reported greater pain interference compared with those with higher health literacy [36].

24.3.8 Income

As with educational attainment, lower income has been identified as a correlate of reduced QOL across several domains including physical (fatigue, pain), social and emotional domains as well as financial difficulties imposed by CRC [29, 35, 36].

24.3.9 Lifestyle

Not only are certain lifestyle factors identified as risk factors for CRC, they have also been shown to be associated with QOL outcomes. Regular physical activity and a diet of at least five portions of fruit and vegetables per day are associated with greater ability to manage fatigue and distress [37, 38]. Conversely, health behaviours such as smoking and excessive alcohol consumption are associated with lower QOL [38, 39]. These lifestyle factors feature predominantly in cancer prevention recommendations and are also pertinent for people living beyond a cancer diagnosis and have been integrated into survivorship care packages alongside monitoring for signs of recurrence and management of long-lasting and late effects of treatment.

24.3.10 Psychosocial Factors

Findings from the Colorectal Wellbeing Study (see Research in focus) suggest that psychosocial factors match or even exceed clinical factors in terms of the role they play in QOL outcomes [12, 24]. In particular, confidence to manage problems relating to CRC (self-efficacy), depression, which was identified above as an important comorbidity in terms of its impact on QOL, levels of positive and negative affect and perceived unmet needs (physical, psychological and health system or information) and social support have been identified as playing a key role in adjustment following CRC [12, 24, 40, 41]. The way in which people face the challenges posed by CRC and its treatment and the resources available to them, for example, social and health care networks, thus might determine QOL outcomes. In this way, individuals matched according to cancer type, stage and treatment protocol are not likely to report similar outcomes given the complex interplay of psychosocial factors.

24.4 Impact of QOL on Outcomes

QOL has been identified as a prognostic factor with higher QOL associated with longer survival particularly in the context of advanced CRC and in older populations [42, 43]. Good symptom management and better psychosocial adjustment to CRC have been associated with better survival; however, it is important to exercise caution when interpreting studies looking at the relationship between QOL and outcomes given the potential interaction of other factors such as disease stage [44].

24.5 QOL Measurement in CRC

24.5.1 Rationale for QOL Assessment

Alongside traditional clinical trial endpoints of clinical response, disease-free, progression-free and overall survival, patient-reported outcomes such as QOL are also integral to the evaluation of new drugs [9]. In addition to clinical trials, QOL assessment can also make a significant contribution within the clinical practice setting. The widespread and often persistent QOL concerns experienced by people with CRC need to be monitored to allow for effective disease and toxicity management beyond physical symptoms to also address psychosocial problems. QOL assessment can also facilitate patient–clinician communication by serving as a conduit to discuss problems that matter to the patient as well as supporting treatment decision-making. In the earlier section of this chapter, it was indicated that physical and psychosocial sequelae of CRC persist well beyond the end of treatment; thus, there is merit in monitoring QOL throughout the disease and survivorship trajectory. In the UK, as part of the NHS Long Term Care Plan to offer personalised care

packages, holistic needs assessment of patients firstly at diagnosis and then at repeated timepoints helps identify areas of concern and support needed for patients and their carers across a number of domains including physical, psychological, social, spiritual and financial. QOL assessment tools can help support this activity.

Research highlighting a lack of alignment between clinician and patient evaluation of the impact of symptoms, for example, bowel dysfunction in CRC [45], adds further weight to the importance of QOL assessment as a means of communicating problem areas where support and intervention are needed and which would otherwise be overlooked. Measuring QOL thus can help health care professionals understand the impact of CRC and its treatment from the perspective of the patient. This lack of congruence in patient and clinician perspective also suggests that QOL assessments need to be carried out by the patient.

Not only can QOL assessment help quantify the impact of CRC and its treatment on the patient and signal areas in need of intervention, the potential prognostic value of QOL data also underlines the importance of implementing QOL assessments as part of clinical practice.

24.5.2 CRC-Specific Measures of QOL

Generic health-related QOL instruments are designed to capture the impact of illness (not just cancer) or cancer in general irrespective of tumour site, and while they allow for comparisons across disease groups, they lack sensitivity to the unique issues of a specific cancer type such as CRC. Two of the most widely used instruments appropriate for CRC include core generic cancer-related questions supplemented with a CRC-specific subscale or module. The Functional Assessment of Cancer Therapy-Colorectal (FACT-C) [46] combines specific concerns related to CRC with concerns that are common to all cancer patients as assessed with the FACT-General (FACT-G) [47] (see also Chap. 6, this volume). The European Organisation for the Research and Treatment of Cancer (EORTC) core cancer measure (EORTC QLQ-C30) [48] is also supplemented with a CRC-specific module (EORTC QLQ-C38, updated to EORTC QLQ-CR29) [49] (see also Chap. 5, this volume). Table 24.1 identifies the QOL dimensions covered by these measures as well as other measures which have been specifically developed for CRC or colorectal disease to include CRC. An investigation of functional outcomes and QOL in people treated with curative intent for rectal cancer [5] which used the FACT-C identified limitations in the interpretations which could be drawn from the data, for example, in making comparisons between patients with and without a stoma and in interpreting the impact on CRC sexual function. The authors proposed that the EORTC QLQ-CR29 would have provided the opportunity for more extensive analysis with its separate stoma and non-stoma questions and the inclusion of four questions (two each for males and females) relating to sexual interest, pain and erectile dysfunction.

While the FACT and EORTC colorectal-specific instruments were developed and validated with people from different cultural and language backgrounds, the Quality of Life Instruments for Cancer Patients – Colorectal Cancer is more cultural-specific and designed for people within China [50]. Two measures focus on QOL issues related to the post-operative period to address the impact of treatment and complications [51, 52]. The Cleveland Clinic Colorectal Cancer Quality of Life Questionnaire (CCF-CaQL) [51] is specific to people who have undergone surgery for CRC, while the Post-operative Quality of Life Questionnaire (PQL) [52] is more generic in terms of proposed suitability for people with colorectal conditions, not just CRC. The authors of the latter two measures criticise the FACT-C and EORTC QLQ-CR29 for their length and potential redundancy of questions, for example, the EORTC measurement strategy requires patients to complete 30 questions from the core measure and 29 (originally 38) CRC-specific questions. The CCF-CaQL and the PQL include 24 and 14 questions, respectively. However, while the FACT and EORTC development and validation processes are robust and rigorous and thus labour and time intensive, the CCF-CaQL and the PQL were developed relatively quickly with mini-

Table 24.1 CRC-specific QOL measures

Measure	Focus	Number of questions	Subscales
EORTC Quality of Life Questionnaire Colorectal Cancer Specific (EORTC QLQ-CR29) [49]	Tumour-specific module to supplement the EORTC QLQ-C30 to measure the QOL concerns in CRC	29	Urinary frequency Blood and mucus in stool Stool frequency Body image Single items: urinary incontinence, dysuria, abdominal pain, buttock pain, bloating, dry mouth, hair loss, taste, anxiety, weight, flatulence, faecal incontinence, sore skin, embarrassment, stoma care problems, sexual interest (men), impotence, sexual interest (women) and dyspareunia
Functional Assessment of Cancer Therapies – Colorectal (FACT-C) [46]	QOL concerns pertinent to CRC combining questions from the generic cancer questionnaire FACT-G with a CRC subscale	36	Physical well-being Social/family well-being Emotional well-being Functional well-being Colorectal cancer subscale
Quality of Life Instruments for Cancer Patients – Colorectal Cancer (QLICP-CR) [50]	QOL in CRC patients in China combining a general module (Quality of Life Instruments for Cancer Patients – General Module QLICP-GM) and a CRC-specific domain	46	Physical Psychological Social Common symptoms and side effects CRC specific
The Cleveland Clinic Colorectal Cancer Quality of Life Questionnaire (CCF-CaQL) [51]	Post-operative QOL following CRC surgery	24	Physical (physical activity and physical health) Mental (emotional and social) Overall score
Post-operative Quality of Life Questionnaire (PQL) [52]	Post-operative QOL in patients with colorectal disease in general encompassing the previously validated CGQL score to facilitate and standardise assessment of recovery after major colorectal surgery	14	Global QOL Nausea Pain Bowel function Return to normal health
City of Hope Colorectal Cancer Quality of Life – Ostomy Questionnaire [53]	QOL in patients with an ostomy	90	Physical well-being Psychological well-being Social well-being Spiritual well-being
Ostomy Concerns Scale [54]	Concerns of cancer patients with ostomies and of their partners	48	Total score
Stoma Care QOL Scale [55]	Developed from the Stoma Care QOL Index to assess QOL in people with colorectal disease with a colo-, ileo- or urostomy	20	Sleep Sexual activity Relations to family and close friends Social relations outside family and close friends
Stoma QOL Scale (SQOLS) [56]	Impact of a stoma on QOL	21	Work/social function Sexuality/body image Stoma function Single items: financial impact, skin irritation and overall satisfaction

mal patient input and validation: the PQL is the result of the work of six surgeons and a subsequent review by 20 patients. Some measures include questions to be completed only by people who have a stoma. The EORTC QLQ-CR29 [49] includes a sub-section with seven such questions. Table 24.1 outlines four stoma-specific measures [53–56] which ask about the broad QOL concerns related to having a stoma, that is, beyond the physical impact to include the psychosocial issues reviewed earlier in this chapter. In a review of ostomy-related problems in people with CRC [15], the City of Hope Colorectal Cancer Quality of Life (COH-QOL) – Ostomy Questionnaire with its 41 QOL impact questions [53] was identified as the most comprehensive.

With the exception of the Ostomy Concerns Scale [54], all measures presented in Table 24.1 are multi-dimensional; thus, they allow for the calculation of summary scores across the different QOL domains such as physical (pain, skin problems, physical function, bowel and urinary problems, sexual dysfunction), psychological (body image, embarrassment) and social (relationships with family and friends) as well as single-item scores such as financial impact and an overall global score. The COH-QOL-Ostomy Questionnaire [53] also includes a spiritual well-being domain.

In summary, several disease-specific measures are available to measure the QOL of people living with and beyond CRC. Such measures include questions likely to be relevant across different cancer types, as well as questions, which are more relevant for people diagnosed with and treated for CRC. In addition, the specificity of questionnaires can be further refined to be relevant to a certain CRC sub-group, such as people with a stoma.

24.6 Interventions to Manage the Impact of CRC and Its Treatment

As mentioned above, QOL plays an important role in determining outcomes in CRC in terms of survival and response to treatment, and QOL itself can be regarded as a marker of good adjustment. Information relating to the predictors of poor QOL can be utilised to inform interventions with a focus on addressing potentially modifiable factors, such as lifestyle, self-efficacy and symptom management. Traditionally, interventions for CRC have been introduced post-operatively to facilitate recovery; however, recently prehabilitation programmes designed to help prepare patients physiologically and psychologically for surgery have become more commonplace with promising outcomes in terms of enhanced surgical recovery and reduced complications [57, 58].

24.6.1 Lifestyle

Physical activity programmes can help improve treatment tolerance as well as managing side effects such as fatigue, pain and insomnia as well as reducing levels of depression and anxiety [59]. Nutritional interventions, for example, dietary counselling has been shown to improve gastrointestinal function and to provide some level of protection against treatment-related toxicity [60]. Evaluations of interventions to promote health behaviours such as exercise and healthy eating have however produced mixed results [61, 62], suggesting that one size does not fit all and that a more personally tailored and combined intervention approach incorporating psychosocial elements might be the optimal strategy to adopt.

24.6.2 Education

A review of psychosocial interventions for people with CRC identified education interventions addressing information support needs (using different modalities, such as home visits, telephone calls, provision of written and electronic materials) as the most common type [63]. Education is an integral part of prehabilitation programmes to prepare for surgery and recovery and is also incorporated within interventions delivered across the treatment and recovery trajectory in response to differing

patient needs over time. A recent longitudinal evaluation of the implementation of a personalised written education and communication intervention revealed positive results in terms of knowing where to go to access support, making sense of recovery, shorter post-operative hospital stays and better QOL [64]. Within the context of stoma management, information, education and preparation can facilitate acceptance, adjustment and stoma proficiency [65].

24.6.3 Cognitive-Behavioural Therapy

Cognitive-behavioural therapies have been used in CRC to mobilise health behaviours such as physical activity, weight management, alcohol reduction and smoking cessation as well as promoting more adaptive coping skills and facilitating better symptom control, for example, fatigue management [63]. Progressive muscle relaxation training sessions have also been used to reduce anxiety and improve QOL following stoma surgery in CRC [66] (see also Chap. 20, this volume).

24.6.4 Communication

Interventions can facilitate the transaction between the person with CRC and health care professionals as well as serving as a platform for emotional expression and a sharing of experiences with other people with CRC. A combined written and verbal disclosure expression intervention ("Healthy Expressions") was well received amongst people with CRC screened for distress, and recipients of this programme experienced less distress over time and better QOL compared to people receiving standard care [67]. The positive effects of such expressive interventions might be mediated by cognitive processing through a reappraisal of experiences or by social support from people who are travelling along a similar path.

24.6.5 Self-Management

Self-management programmes incorporate elements of the above interventions to empower people to adopt an active role in the management of their cancer and the effects of treatment. Throughout the disease and treatment trajectory as well as the post-treatment period, this might involve being an active participant of the decision-making process, reporting and managing side effects (including late effects) or signs of recurrence, goal setting and engaging in lifestyle changes to reduce the physical symptoms and psychosocial sequelae of CRC and its treatment, and improve QOL. Within CRC survivorship care packages, self-management programmes have been implemented and have demonstrated feasibility and effectiveness, but evaluations of such programmes need to be further developed.

24.6.6 Summary

Interventions are designed to improve outcomes such as symptom management, distress and QOL by addressing physical and psychosocial modifiable factors which are known to play a role in the experience of CRC and its treatment [63]. Interventions introduced early in the CRC pathway help people prepare for treatment and recovery by providing information regarding what to expect, where to access support and how to manage problems which might arise from CRC and its treatment. Evidence to support the feasibility and efficacy of such interventions is limited and where favourable outcomes of interventions are presented, they are often criticised for their sample bias as well as incomplete information regarding the nature and delivery of the interventions. In addition, recommendations for the optimal timing and type of CRC interventions have not been clearly established. It has been proposed that future research should focus on evaluating the effectiveness of a blend of different psychosocial interventions and the role of family members/caregivers in the implementation of interventions.

24.7 Conclusion

The physical and psychological consequences of being diagnosed and treated for CRC overlap with other cancer types, for example, fatigue, pain, depression and anxiety, but for this patient group, there are also some specific morbidities and QOL concerns. Physical and psychosocial problems relating to bowel function are a particular hallmark for this patient group and the placement of a stoma also introduces a unique set of concerns. Treatment either in the neoadjuvant or in the adjuvant setting with chemotherapy and radiotherapy also presents toxicities and the potential for structural damage impacting on bowel, urinary and sexual function. While the effects of CRC might be experienced more acutely early in the disease and treatment trajectory, CRC can leave a long-lasting physical and psychosocial legacy compromising QOL not just in the short term. While we can generalise to a degree with respect to possible outcomes for people with CRC, there is variability in patient experience which is not just determined by disease and treatment parameters but also person-specific characteristics which go beyond those relating to socio-demographic status to include psychosocial factors, for example, self-efficacy, social support, QOL at diagnosis and physical status. The importance of QOL assessment has increasingly become recognised within both the clinical trial and clinical practice settings. There is not one gold standard QOL measure for CRC, and often the choice of instrument is driven by area of interest. QOL assessment allows for close monitoring and timely management of QOL concerns, which might involve modifications to treatment schedules or implementation of psychosocial interventions to improve QOL outcomes. Personalised support services to address the unique QOL concerns of people with CRC patients are an important goal for clinical care and future research endeavours.

24.8 Questions that Can Be Used for Learning/Testing

- For patients with operable cancer, what factors need to be considered when considering the benefits of introducing short-course preoperative radiotherapy or chemoradiotherapy?
- Can we identify patients who are likely to need more help following a diagnosis of CRC?
- How can we modify the risk factors for poor QOL?
- How can we identify "at risk" patients for poorer QOL outcomes?

24.9 A Topic for Discussion that Can Be Used for Teaching

To what extent can CRC be regarded as a chronic condition?

24.10 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

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24.11 Research in Context

A longitudinal cohort study to explore recovery of health and well-being of people affected by colorectal cancer

Objectives

Plot the natural history of recovery of health and QOL from the point of diagnosis to 5 years post-treatment for CRC treated with curative intentInvestigate whether/how health needs change over timeExplore what influences recovery of health and QOL and determine who is most at risk of poor/protracted recoveryChart the utilisation of health care services and explore relationship with recovery of health and well-beingDescribe the use of self-management techniques, factors related to self-management and its relationship with recovery of health and well-being*Method*Patients with a diagnosis of CRC (Dukes Stage A-C) were asked to complete questionnaires at baseline (pre-surgery in most cases), then at 3, 9, 15, 24, 36, 48 and 60 months later.Questionnaires asked about (for a full list of measures, please see the protocol paper [*68*]):QOL including symptoms and functioning and well-beingHealthSelf-efficacy/confidence to manage CRCSocial supportPositive and negative affectDepression and anxietyCoping strategiesSupportive care needsHealth service useSocio-demographicsClinical and treatment characteristics*Results*A representative cohort of 1017 non-metastatic CRC patients were recruited from 29 UK cancer centres.At least one follow-up timepoint, 60% of patients had worse QOL compared with baseline and around one-third did not return to pre-surgery levels of QOL during the 5 years following treatment. There was a significant improvement in QOL at 15 months post-surgery but little change after that point. Participants with rectal cancer had lower levels of QOL [*24*].This study showed that psychosocial factors before surgery predict recovery trajectories in QOL, health status and well-being following CRC treatment, independent of treatment or disease characteristics [*12*].Baseline factors associated with worsened QOL included neoadjuvant treatment, presentation of two or more comorbidities, high negative affect and low levels of confidence to manage the effects of CRC, low levels of social support and positive affect [*24*]. Patients' perception of unmet needs, particularly physical, psychological and health system, and informa-

tion needs were also associated with poorer overall QOL at the end of treatment [*41*].Pre-treatment QOL itself was associated with poorer outcomes in terms of the perception of unmet needs [*41*] and poorer social support [*40*].

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Quality of Life and Endometrial Cancer

25

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25.1 Introduction

This chapter will enable the readers to (a) better understand the different quality-of-life parameters to assess, interpret, and link for better patient outcomes; (b) know about the various health-related quality-of-life (HRQOL) assessment tools that can be used in clinical trials and management of cancer patients, especially in endometrial cancer (EC); and (c) know about the importance of linking clinical trials data with quality-of-life outcome parameters for better treatment choices.

25.2 Definitions

Endometrial cancer or cancer of the corpus uteri is cancer that arises from the epithelial lining of the uterine cavity.

25.3 Epidemiology (Second Cancer in the List of 5-Year Survival Rate)

Endometrial cancer is the most common female gynecological cancer in the US, with 65,620 new cases in 2020. It is ranked 17th in the number of new cases of all cancer cases globally in 2020, with 417,367 new cases and 97,370 new deaths [1, 2].

25.4 Etiology

Endometrial carcinomas are characterized by various genetic alterations, but the most frequent alteration is in the PTEN gene, located on chromosome 10q23 [3, 4], in addition to alteration in p53 gene, located on chromosome 17 [5, 6].

25.5 Histopathology

25.5.1 Histopathological Types

There are seven histopathological types of endometrial cancer verified microscopically. They are endometrioid carcinoma (adenocarcinoma), mucinous adenocarcinoma, serous adenocarcinoma, clear-cell adenocarcinoma, undifferentiated carcinoma, neuroendocrine tumors, and mixed carcinoma [7].

25.5.2 Histopathologic Grades

There are three histopathological grades of endometrial carcinoma, from 1 to 3, in addition to GX that stands for the inability to assess the sample. The grading scores are [7]:

1. G1: Well-differentiated (less than 5% of a non-squamous or non-morular solid growth pattern).

2. G2: Moderately differentiated (6–50% of a non-squamous or non-morular solid growth pattern).
3. G3: Poorly or undifferentiated (more than 50% of a non-squamous or non-morular solid growth pattern).

25.6 Risk Factors

Changes in the balance of female hormones, such as conditions with excess estrogen, for example, estrogen-secreting tumors and hormone replacement with unopposed estrogen (i.e., estrogen therapy without progesterone) [8, 9], more years of menstruation, nulliparity, old age, obesity [10], Tamoxifen [11, 12], conditions associated with metabolic syndrome [13], diabetes [14], polycystic ovary syndrome [15, 16], and Lynch syndrome (also called hereditary nonpolyposis colorectal cancer (HNPCC)) [17, 18].

25.7 Clinical Picture

Endometrial cancer mostly present symptomless or with nonspecific symptoms, such as vaginal bleeding after menopause and bleeding between periods and pelvic pain [19].

25.8 Diagnosis

Screening of endometrial cancer is only recommended for high-risk groups, such as those with Lynch syndrome with a wish for fertility preservation before opting for a prophylactic hysterectomy at a later age. The routine screening is performed by aspiration biopsy and transvaginal ultrasonography starting from the age of 35 years and annually until hysterectomy [7].

Transvaginal ultrasound is an effective first-line investigation with a high negative predictive value for endometrial thickness less than 5 mm. Combining transvaginal ultrasound and endometrial sampling by curettage has a negative predictive value of 96%. After the histopathologic diagnosis of endometrial carcinoma, other factors must be assessed, which include the local extent of the tumor, metastases, and perioperative risk [7, 20].

If the ultrasound is suggestive of endometrial cancer, other investigative tools can be used, such as curettage for endometrial sampling, saline infusion sonohysterography, and hysteroscopy. MRI can be useful in providing additional information on endometrial thickening or for the exclusion of structural abnormalities such as fibroids or adenomyosis [21].

For follow-up, serum CA125 may be of value in advanced disease [7].

25.9 Treatment Modalities

The International Federation of Gynecology and Obstetrics (FIGO) staging system first appeared in 1958. It targets risk-stratifying patients into multiple stages according to the degree of tumor spread and metastasis, as recurrence rates, overall survival, and individual outcomes are directly related to the degree of tumor spread at the initial presentation. Several treatment regimens have been proposed including a plethora of treatment modalities.

Surgery: Most endometrial cancer (EC) patients are at an early stage, namely, FIGO stage I. However, the exact management plan should include intraoperative and histopathological findings [22]. For stage I of the disease, total hystrectomy without colpectomy along with bilateral salpingo-oophorectomy is the standard of care [23], minimally invasive approaches as laparoscopy have been proposed with much better postoperative complication rates and lower frequency of hospital stay [24]. Robotic surgery gaining ground now in many centers is mostly used in difficult contexts for traditional surgery such as morbidly obese patients [25]. Traditional surgical staging in the past involved complete pelvic and para-aortic lymphadenectomy; however, European Society for Medical Oncology guidelines do not recommend routine lymphadenectomy for low-risk grade 1 or 2 disease [26].

Although around 80–85% of EC patients are diagnosed at an early stage, 10–15% will have advanced disease at presentation, treatment plans are mainly derived from and similar to ovarian cancer treatment. Cyto-reduction to less than 2 cm residual disease has been correlated with survival benefit, and best results are gained when no visible disease remained [27]. For patients who are not eligible for optimal cyto-reduction, neoadjuvant chemotherapy may be tried with various treatment results [28].

Radiation therapy: Radiotherapy (RT) can reduce the risk of local recurrence of the disease, but randomized clinical trials (RCTs) have not demonstrated overall survival (OS) benefits in early-stage disease [29]. Furthermore, adjuvant therapy to the whole pelvis may lead to major adverse events limiting the quality of life of the patient such as urinary incontinence, fistulae and fecal leakage [29]. However, for high-risk patients (grade 3, grade 1 or 2 with age more than 60 years and/or lympho-vascular involvement) but still presenting as early-stage disease, vaginal brachytherapy (VBT) offers better local control with fewer adverse events, when compared to external beam radiation therapy (EBRT). Locally advanced disease is usually treated with EBRT to target local nodes at risk. However, the decision for adjuvant therapy as well as the best modality remains a controversial topic [23].

Chemotherapy: Chemotherapy in the context of EC remains a controversial topic; however, proper selection of the patients may maximize the benefits. Traditionally, chemotherapy was used mainly for serous-type tumors and stage III or higher tumors of any histological type, with carboplatin and paclitaxel regimens as the most commonly used regimen [23]. GOG 249 trial was conducted to investigate whether chemotherapy with vaginal brachytherapy was superior to adjuvant pelvic radiation therapy in patients with early-stage disease, and both arms had comparable recurrence-free survival, similar vaginal and distant recurrences [30]. GOG 122 trial compared chemotherapy with adjuvant RT in the context of more advanced endometrial cancer (stage III and stage IV); patients who had chemotherapy had better progression-free survival and overall survival. This study documents the benefits of chemotherapy in advanced disease [31].

Endocrine therapy: Patients with more differentiated tumors and estrogen receptor-positive disease are more likely to benefit from endocrine therapy, which signals the importance of proper patient selection. Many old randomized trials failed to show the benefits of using progestins in the adjuvant settings; however, they can be used in metastatic disease with a reasonable margin of benefit [23]. The usage of progestins alternating with tamoxifen regimens can result in response rates ranging from 27% to 33% [32].

Palliative care: The Society of Gynecologic Oncology (SGO) released recommendations that encourage implementing highly qualified clinical care during the course of the disease and through all its treatment stages. It also states the importance of incorporating the principles of palliative care in treatment plans [33]. The Educate, Nurture, Advise, Before Life Ends (ENABLE) II project data analysis indicated that quality of life scores of patients who received palliative care from the time they were diagnosed with cancer were higher than the patients who received standard oncological treatment alone [34].

25.10 The New Era of QoL in Cancer Management

Recently, there is a growing trend of incorporating patient-reported outcomes (PROs) and quality of life (QoL) measurements in research and routine clinical practice. The US Food and Drug Administration (FDA) defines PROs as "any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else." As healthcare is becoming more and more patient-centered, PRO data appears as the guidance for more and more individualized decision-making and policy planning

in the setting of data-driven care [35]. PRO measures were originally designed to help clinical research; however, incorporating them in routine clinical practice may improve patient's outcomes. These anticipated benefits led both FDA and European Medicines Agency (EMA) to highlight the importance of direct patient reporting in healthcare systems because some of the effects of illness are known only to patients and its objective measurement won't be feasible [35, 36].

FDA summarizes the process of generating PRO measure as the following [35]: it first recommends using PRO tool when the concept is best determined by the patient. Then throughout the whole development process, the investigators must provide clear documentation of patient inputs. The instrument must show clear evidence of reasonable performance in the specific application for which it was designed. The process of development must pass through many logical steps (Fig. 25.1):

1. The first step is hypothesis and conceptualization, a framework is designed based on expert knowledge and literature review of similar tools and anticipated PROs; this must also include the rationale for the development of a new tool.
2. The framework should include measurable items, describing some domain-specific function of interest; it must be multidimensional and complex so as not to miss the changes occurring in the real world.
3. After hypothesis and conceptualization, it should be adjusted to patient inputs, making sure that the tool is sensitive enough to capture what matters to the patient.
4. The domains should be tested for reliability, validity, and their ability to detect changes.
5. Development of the instrument is an iterative process, meaning that it is a cyclical process of refining or tweaking the latest version, the version that expresses how things work in the real world in the best possible way. So, the process should be further modified and the cycle repeated.

As resources are becoming limited and treatment costs increased, PRO tools designed should be derived from sound methodological practices and tested to ensure reliability, to guide management plans and decision-making [37]. This urgent

Fig. 25.1 The process of generating PRO measure

need for standardization was addressed in Setting International Standards in Analyzing Patient-Reported Outcomes and Quality of Life Endpoints Data (SISAQOL) Consortium. This review presents a set of recommendations for PROs in cancer RCTs by addressing three main target priorities: designing a research taxonomy to be matched with sound statistical methods, developing specific statistical methods to address PRO objectives, and choosing plans to tackle missing data problems [38].

In 2012, benefit working group sessions on QoL research in clinical trials in EC were held, from which GCIG recommendations emerged. These recommendations stated that [39]:

- QoL data should be collected in all phase III trials, either as a primary or as a secondary outcome, in all types of treatment (first-line, maintenance, recurrent, and palliative) and across all risks (low-, intermediate-, and high-risk patients).
- QoL data and PROs should be collected through validated tools, stating the importance of the cyclical process of refining and tweaking the tools, and collection should be based upon generic or cancer-specific tools (see later).
- As many studies suffered from the late publication of the data limiting its values, PRO data should be published within the same time frame of all EC trials.
- Sound statistical methods should be used, correcting for all confounders and biases in EC like body mass index (BMI), age, and comorbidities.

25.11 Patient-Reported Outcome Versus Traditional Healthcare Metrics

By time, medical care became more diverse and complex involving many diagnostic options and treatment modalities. Although this was associated with improved outcomes across many medical nosologies, unfortunately, this distanced physicians from their patients. A landmark paper by Barry et al. [40] pointed out this problem: the recent advances resulted in a healthcare environment that excluded the patients and their families, leaving them in the darkness not knowing how their conditions are being managed. Traditional healthcare metrics usually used parameters and surrogates like mortality rates, length of hospital stay (LOS), and readmissions. Although these parameters are important in designing treatment plans, they often overlook the direct questions that impact patients' quality of life. So traditional metrics should go hand in hand with PROs in shared decision-making, the clinician presents options explaining their risks and benefits, and the patient chooses what is suitable for his preferences and values [41], so the patients have better imagination of all the relevant factors and actively participate in decision-making.

As mentioned before, GCIG recommends incorporating QoL data in all subsequent EC trials either as primary or as "double primary" endpoint. As many EC patients are diagnosed at an early stage and the cure is the main intent, QoL may be an appropriate secondary endpoint when compared with the traditional metrics as survival and recurrence rates [39]. Unfortunately, in some patients, cure is not possible and palliation is the primary intent, as in cases of recurrent EC; here, QoL may be the primary endpoint with the target of relieving patients' symptoms. Collecting these data should be standardized, as a high proportion of missing data could be prevented by well-conducted study designs; however, these studies can be challenged with many logistical difficulties in collecting data, particularly in patients who need long follow-up or have a poor prognosis [42].

25.12 Tools Used to Assess QoL (Their Calibration, Validation, and Comparison Among Them)

Measurement of health-related quality of life (HRQOL) involves assessment of consequences of medical and surgical issues on the physical,

Table 25.1 Health-related quality-of-life (HRQOL) assessment tools

Tool name	Type	Domains and scales	Languages available
EORTC QLQ-C30	*Generic*	5 functional scales (physical, social, emotional, cognitive, and role) 9 symptom scales (pain, fatigue, nausea, vomiting, dyspnea, sleep, appetite, constipation, and diarrhea) 1 financial scale	86 languages
EORTC QLQ-EN24	*Cancer site specific*	6 sub-scales (lymphedema, urological symptoms, gastrointestinal symptoms, body image, sexual function, and vaginal symptoms)	11 languages
FACT-G	*Generic*	4 domains (physical well-being, social/family well-being, emotional well-being, and functional well-being)	60 languages
FACT-EN	*Cancer-site specific*	1 domain (problems related to EC such as vaginal bleeding and discharge, hot flushes, discomfort with intercourse, etc.)	8 languages

emotional, and daily lives of the patients [43]. There are two basic types of measurement of HRQOL—generic and disease/population specific. Generic measures apply domains that could be used indifferently to many populations, ethnicities, and diseases; however, this wide range of capabilities limits its specificity in disease-specific dimensions. Disease/population-specific measures, on the other hand, are designed specifically for certain diseases and populations, which maximizes its sensitivity, specificity, and ability to detect minute changes; however, they can't be used in comparing various HRQOL results across populations and various diseases [44].

Selecting "what matters the patient" as a surrogate is manifested in the assessment of sexual health. For example, Sexual difficulties after treatment with gynecologic cancer affect between 30% and 100% of survivors and represent one of the most distressing long-term sequelae of cancer [45]. Previous studies incorporated surrogates like sexual intercourse frequency, dyspareunia, and orgasmic capacity [46]. However, these surrogates may not be accurate and aren't truly reflecting what is occurring in the real world, for example, one patient may increase intercourse frequency for reasons that is not related to her drive for sex: wishing to please a partner, for example.

The standard-of-the-art approach in clinical trials now is combining both generic questionnaires with cancer site-specific scales. The most widely used generic questionnaires in EC are the European Organization for Research and Treatment of Cancer Quality of Life Questionnaire 30 (EORTC QLQ-30) and the Functional Assessment of Cancer Therapy General (FACT-G) measurement system. Cancer site-specific modules are often used as supplements to more general questionnaires; The European Organization for Research and Treatment of Cancer Quality of Life Questionnaire-Endometrial Cancer 24 (EORTC QLQ-24) and Functional Assessment of Cancer Therapy-Endometrial (FACT-EN) are examples of site-specific modules in EC. A summary of the most widely used tools is given in Table 25.1 [42, 47]:

25.13 Endometrial Cancer-Associated Baseline Comorbidities Influencing QoL

25.13.1 Obesity

Endometrial cancer has a strong association with obesity. Females with a normal body mass index (BMI) have a 3% lifetime risk of endometrial cancer, but for every 5 kg/m^2 increase in the BMI, the risk of cancer increases by more than 50% [10, 48, 49].

The increased risk of endometrial cancer in obese women might be explained by more than one mechanism. There are higher rates of conversion of androgenic precursors to estradiol by increased aromatase enzyme activity in adipose tissue. The increased estradiol does not only increase endometrial cell proliferation and inhibits apoptosis, but can also stimulate the local synthesis of IGF-I in endometrial tissue. Furthermore, chronic hyperinsulinemia might catalyze tumorigenesis in estrogen-sensitive tissues, as it reduces blood concentrations of sex-hormone-binding globulin, which will consecutively increase bioavailable estrogen [10].

Obesity is associated with poorer quality-of-life outcomes in endometrial cancer survivors, resulting in poorer physical, role, and social functioning. These quality-of-life parameters decline even further as BMI increases [50]. However, using EORTC-EN24, Oldenburg et al. found an inverse relationship between body mass index (BMI) and sexual/vaginal problems, such as vaginal dryness [51].

25.13.2 Hypertension

Several studies correlated having hypertension, even controlled hypertension, with a 61% increase in the relative risk for endometrial cancer [52, 53]. However, further research is needed to confirm the correlation, as hypertension's risk factors are shared with other risk factors for developing endometrial carcinoma, such as diabetes and obesity.

25.13.3 Old Age

The incidence of endometrial cancer increases steadily with age from a 1 in 166 probability in the sixth decade of life to a 1 in 75 chance by the eighth decade [54]. Older age was found to be a significant predictor of poor disease-free survival. This influence of advanced age is independent of other poor prognostic factors such as deep myometrial invasion or aggressive histology [55].

The geriatric condition itself affects the prognosis and quality of life by limiting the management options for elderly patients. As many elderlies have several chronic depleting diseases (hypertension, diabetes, ischemic heart disease, chronic kidney disease), in addition to living a sedentary life without a healthy nutrition plan, all these factors have a dramatic magnitude on their quality of life [56, 57].

25.14 Treatment Modalities' Effect on QoL

There is a growing trend of recognizing the importance of reporting PROs and QoL data in all EC trials irrespective of its stage or disease spread [58]. Most patients have a favorable prognosis with overall survival reaching 90%, so late effects of the treatment must be taken into consideration when designing a treatment plan. Surgery and radio-chemotherapy may confer short- and long-term limitations to QoL. The following section gives a brief discussion about these problems.

25.14.1 Surgery

Hysterectomy: Minimally invasive approaches like laparoscopy and robotic-assisted surgery are now replacing traditional laparotomies. GOG LAP-2 trial [24] is a phase III randomized clinical trial that enrolled 2616 participants for comparing laparoscopic vs standard surgery in surgical staging of the patients with EC; of these, 802 patients participated in QoL study [59]. The study used FACT-G score; laparoscopy patients had better early QoL, better physical functioning, less postoperative pain, early resumption of activities, and overall better QoL in the first 6 weeks, but QoL scores at 6 months were similar for both treatment arms apart from body image, which was better in the laparoscopy arm. LACE trial is also a phase III randomized clinical trial that enrolled 760 participants, of which 332 patients participated in QoL sub-study [60]. This study also used FACT-G score; in the early stages of recovery, patients who had a total laparoscopic hysterectomy (TLH) had better QoL scores when compared to total abdominal hysterectomy (TAH), confirming the findings from the GOG LAP-2 trial. However, at 6 months,

LACE study found that QoL scores are still better in the TLH arm, except in emotional and social well-being measures which were comparable. Head-to-head comparisons between robotic-assisted surgery and traditional laparoscopy were compared in a recent meta-analysis [61]; however, the main focus was on traditional metrics like length of hospitalization, blood loss, and lymph node harvesting with no QoL data.

Lymphadenectomy: As mentioned before, European Society for Medical Oncology guidelines do not recommend routine lymphadenectomy for low-risk grade 1 or 2 disease. However, for high-risk patients, the SEPAL study showed that the patients who had pelvic and para-aortic lymphadenectomy had better overall survival justifying its use in this special context [62]. The data on the effects of lymphadenectomy on QoL remains scarce. A study by Angioli et al. found that among all symptom scales, only lymphedema was statistically significant among the group who had lymphadenectomy; other measures in "Global Health Status" wasn't statistically significant, so they supported its routine practice in high-risk patients [63]. Another cross-sectional, population-based study confirmed that patients who had lymphadenectomy were more liable for developing lymphedema, and scores were related to the number of lymph nodes affected [64].

Radiotherapy: The Post-Operative Radiation Therapy in Endometrial Cancer Trial PORTEC-2 is a multicenter randomized trial; 427 patients were enrolled and assigned to either external beam radiotherapy (EBRT) or vaginal brachytherapy (VBT). Of these, 348 who participated in QoL sub-study and followed up for 2 years; EORTC QLQ-C30 was used in the assessment. Patients in the VBT arm had better social functioning and lower symptomatic scores for diarrhea, fecal leakage, the need to stay close to the toilet, and limitation in daily activities because of bowel symptoms [65]. A smaller study that followed the patients who received radiotherapy after 2 years found that although HRQOL was at its worst directly following the treatment, QoL improved during the follow-up but was worse in the patient who had progressive disease or recurrence [66]. In VBT, dosing regimens when designed more precisely could further reduce the toxicity of the treatment.

Chemotherapy: PORTEC-3 trial is a multicenter and international trial. Women with high-risk features were randomly allocated to receive either radiotherapy alone or radiotherapy combined with adjuvant chemotherapy; EORTC QLQ-C30 was used in this trial. After the treatment and at 6 months, chemoradiotherapy arm reported worse functioning and symptoms; however, at 12 and 24 months, the results were comparable between the two arms [67].

25.15 Conclusion

With the steady expansion in medical knowledge, patients were left excluded from decision-making and their inputs were ignored. Patients' perspectives, although different from traditional matrices, remain an important pillar to be included in modern medical care. Hence, more awareness of the topic shall be given from all health institutes and healthcare providers. Having patient-centered management plans will achieve more patients' satisfaction and improve their quality of life after the diagnosis of endometrial cancer.

25.16 Questions That Can Be Used for Learning/Testing

1. Is there a way to further integrate quality-of-life parameters into routine practice?
2. Eurocentrism: Are the current available health-related quality-of-life (HRQOL) tools globally valid?

25.17 A Topic for Discussion That Can Be Used in Teaching

- Patient-centricity approach in modern medicine.

Medicine was limited for decades, as prevalence rates, mortality numbers and efficacy of cer-

tain procedures in treating or curing diseases, and prioritizing patient' life length over their quality of life. We are in a new era in which management plans are put differently. Patient's needs, choices, and perspectives are highlighted in order to assure the quality of modern healthcare stands out.

- Objective tools vs subjective symptoms, the dilemma of standardization.

Having a standardized tool to assess subjective symptoms is an issue with a long history in the medical sciences. Medical nosologies depended on metrics that could be accurately measured, classified, organized, and standardized, a dilemma facing QoL assessment and its subjective inputs. It is crucial to identify the obstacles coming ahead and finding solutions for them.

25.18 Further Reading List

- Quality of Life Among Cancer Survivors: Challenges and Strategies for Oncology Professionals and Researchers, Tanya R. Fitzpatrick Springer International, 2018, https://doi.org/10.1007/978-3-319-75,223-5
- Effect of cancer on quality of life by David Osoba, CRC Press, 1991, https://doi.org/10.1002/pon.2960010409
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25.19 Research in Context

This systemic review evaluated 1722 studies, of which a total of 27 studies fulfilled inclusion criteria. Sample sizes of the included studies ranged between 38 and 666. A range of PRO tools were used, EORTC QLQ-C30 was included in 9 of the 27 studies reviewed, Short Form 36 Questionnaire (SF-36) was used in 8 studies, FACT-G and Female Sexual Function Index (FSFI) were used in 5 and 4 studies, respectively. Other less known tools were used such as Sexual-Function Vaginal Changes Questionnaire, Euroquol 5-D, and Impact of Events Scale.

As mentioned before, certain baseline comorbidities often complicate EC patients and decrease the overall QoL. Six studies reported lower QoL scores among obese EC survivors when compared to normal weight controls, and one study found that the difference was only statistically significant at certain cut-value (BMI being greater than 40). Diagnostic delay, defined as the number of weeks between first cancer symptoms and the initiation of treatment, was associated with lower overall QoL scores and resulted in worse fatigue, satisfaction, and reduced social function. Emotional distress and higher levels of circulating cytokines (e.g., IL-6) were associated with increase in pain intensity. Active coping, when compared to passive coping, was related to lower mortality, suggesting that counseling not only improves quality of life, but also positively affects traditional metrics such as mortality.

Given the increasing incidence of EC and high survival rates of the disease, more attention should be paid for health-related QoL. PROs are valuable as it comes directly from patient inputs, without re-interpretation of patient responses by the physician or his family members. As our knowledge about PRO increases, more radical changes in standards of care will likely occur, and despite the overall progress in PROs in recent medical literature, more research among EC patients is needed.

R. Shisler et al. (2017) Life after endometrial cancer: A systematic review of patient-reported outcomes. Gynecologic oncology, 148(2), 403–413. https://doi.org/10.1016/j.ygyno.2017.11.007

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Melanoma and Quality of Life

26

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26.1 Introduction

Treatment of each stage of melanoma impacts on the quality of life (QoL) issues experienced by melanoma patients. This chapter will enable readers to: (a) understand treatment of melanoma; (b) identify these issues; and (c) be aware of how QoL is measured for these patients.

26.1.1 Melanoma

Melanoma is a cancer derived from melanocytes of the skin. It is common in people of fair-skinned ancestry, particularly if they reside in areas of high ultra-violet light exposure and is the nineteenth most commonly occurring cancer in men and women in the world with nearly 300,000 new

cases in 2018 [1]. Australia had the highest rate of melanoma in 2018 with 33.6 per 100,000 population, with Northern European countries close behind (e.g. Norway 29.6 per 100,000 population). The UK and US rates were 15.0 and 12.7 per 100,000 population, respectively [1]. It affects more men than women, and older rather than younger people, although it is the most common cancer affecting the 20–40-year-old age group [1].

Melanoma is staged by the American Joint Committee on Cancer (AJCC) 8th Edition staging manual [2], with Stage I and II being melanoma localised to the skin (increasing stage being related to Breslow thickness of the melanoma in millimetres (depth in the skin) and presence or absence of ulceration), Stage III melanoma metastasised to lymph nodes or intransit disease (spread to the skin between the primary site and local lymph nodes), and Stage IV melanoma spread to other organs.

26.1.2 Treatment of Melanoma

The treatment of melanoma at each stage is very different and therefore results in distinct physical and subsequently psychological and quality of life (QoL) issues. The primary treatment for Stage I and II melanoma is surgery taking a wider excision of the local melanoma site. A higher risk primary melanoma may require additional surgery for staging the local draining lymph node(s) with a sentinel lymph node biopsy (SLNB). SLNB uses the concept that cancers drain through the lymphatic system, from the first to subsequent levels. Therefore, the first lymph node encountered (the sentinel node) will most likely be the first affected by metastasis. Lymphoedema (swelling in a limb) may result as a consequence of disrupting lymphatic drainage of the limbs by SLNB, but the risk is low. When melanoma has spread to the local lymph nodes or developed intransit disease, the usual treatment is surgery to resect the metastatic disease. The surgery for patients presenting with palpable lymph node disease is dissection of a particular lymph node field (axilla, groin, or neck), resulting in the challenges of post-surgery healing and lymphoedema (with a risk of complications particularly for groin dissections).

The development of effective new drugs for melanoma has changed the treatment and prognosis of metastatic melanoma significantly; for Stage III disease the use of adjuvant drug therapy following surgery has improved survival from approximately 50% at 5 years prior to use of these drugs to now an estimated 63% at 5 years; for Stage IV disease survival has improved from approximately 10% at 5 years prior to use of these drugs to now at least 50% at 5 years [3], albeit at the risk of significant side effects. There are two new classes of drug for melanoma – targeted drugs (targeting BRAF and mitogen-activated protein kinase [MEK] particular oncogenic abnormalities in the melanoma cell) and immune checkpoint inhibitors (ipilimumab, a cytotoxic T-lymphocyte antigen 4 [CTLA-4] inhibitors, and nivolumab and pembrolizumab, which are programmed death-1 [PD-1] receptor inhibitors). The improvement in survival for both Stage III and IV melanoma has resulted in survivorship challenges for these patients who traditionally would have not survived a diagnosis of metastatic melanoma.

Despite continued progress in the medical management of many malignant diseases, the diagnosis of melanoma remains a fearful and distressing event in the lives of many patients and their families. There are many aspects of a person's life including their work, activities of daily living and family relationships, which disrupted by the diagnosis, treatment, or surveillance of melanoma [4, 5]. These disruptions have the potential to change QoL including daily living, self-identity, body image, and physical and emotional well-being [6]. Impaired QoL has been associated with increased level of fear of recurrence, depression, presence of symptoms burden, and financial difficulties [7].

26.2 QoL Measurement for Melanoma Patients

Historically, and in general terms, QoL for any cancer patient has been an ambiguous and elusive concept [8]. Measurement of the impact on

patients' QoL following diagnosis and subsequent treatment for melanoma has remained a particular challenge. Melanoma is the most serious type of skin cancer, and there is a paucity of evidence on the impact of melanoma on QoL compared to that for other cancers.

26.2.1 Melanoma-Specific QoL Measurements

The scant choice of melanoma-specific instruments may have limited the growth of QoL research involving patients with melanoma [9], compared to other site-specific cancers. Most studies have utilised readily available generic cancer QoL instruments or, on occasion specific instruments developed for non-metastatic skin cancers [10]. The research imperative, therefore, is to continue to focus on the development and validation of a melanoma-specific and clinically relevant quantitative instrument.

Until recently, only two QoL instruments had been specifically designed and validated for use with melanoma patients. The Malignant Melanoma Module [11] entered the public domain over 25 years ago, but it has been very rarely cited in the relevant international research literature. The later FACT-Melanoma (FACT-M) [12] has been more visible over time and was recently subject to Rasch Analysis [13]. Results strongly suggested that confusion existed between patient choices amongst some of the response options, and interpretation was, therefore, variable. Improvements in the structure and response format of the FACT-M for use in future melanoma clinical trials were recommended, but they have yet to be adopted.

The EORTC Melanoma Module (QLQ-MEL38) completed Phase 3 development (pretesting of the preliminary questionnaire) in 2016 [14] which represented a step forward in the measurement of the impact of melanoma on patient QoL (https://qol.eortc.org/questionnaires/). The instrument comprised 33 scoring items in 6 subscales, two single items, and three items associated with clinical trials. However, findings from this study recommended that some items be re-phrased, together with an alteration of the patient's response timeframe. The instrument has not undergone final Phase 4 validation, required to establish validity and reliability for international use. Its suitability for use in patients with advanced melanoma disease who experience a range of new side effects arising during treatment is also limited.

More recently, an international research collaboration has sought to create a new research instrument with the capacity to measure the key areas of concern for melanoma patients managed in the '*usual*' clinic situation and their impact on quality of life. The QLQ-MEL38 was administered to a large sample of melanoma patients, across four countries and three languages. The psychometric properties were analysed and findings suggested a new structure of 29 items across 5 subscales, rather than 33 scoring items across 6 subscales in the EORTC Phase 3 study [15]. Ten items were removed from the QLQ-MEL38, based on a combination of principal components analysis, Rasch, clinical judgement, and face validity. The time frames for response to some items were also amended [15]. The resultant questionnaire consists of a total of 28 items with enhanced psychometric properties. The four scoring subscales (Disease prognosis/acceptance, Treatment concerns/future disease risk, Care delivery/communication, and Supportive Care), together with five individual items, were named the Melanoma Concerns Questionnaire, MCQ-28© for short (Table 26.1).

The subscales measured by this Patient-Reported Outcome Measure (PROM) span several psycho-oncological domains, deemed important to melanoma patients, regardless of disease stage. The measure can be used either as a stand-alone questionnaire, or together with the EORTC QLQ-C30 core questionnaire and/or for patients with experience of treatment for advanced disease, with a symptom-based questionnaire specifically designed to focus on the impact of treatment side effects for melanoma on QoL. It is designed to provide a fresh opportunity for patients to record the psychosocial impact of living with melanoma via routine real-time evaluation of their experience during regular attendance at a melanoma clinic. Once the clinical utility of the MCQ-28 becomes better known,

Table 26.1 MCQ-28 subscales, single items, and their abbreviations

Subscales and abbreviations	Timeframe	Interpretation	Items	Response format
Disease prognosis and acceptance (ACP)	Since the diagnosis and treatment of your melanoma	High score = high QoL	6 items	4-point scale, 1–4
Treatment concerns/future disease risk (CON)	Since the diagnosis and treatment of your melanoma	Low score = high QoL	8 items	4-point scale, 1–4
Care delivery/ communication (CARE)	During the past 4 weeks	High score = high QoL	3 items	Rescored to a 3-point scale*
Supportive care (SUP)	In the last 4 weeks	High score = high QoL	6 items	Rescored to a 3-point scale*
Melanoma surgery site (SURG1, SURG2, SURG3)	For surgery within last 12 months, during the past 4 weeks	Low score = high QoL	3 items	4-point scale, 1–4
Social circumstances (SOC1, SOC2)	During the past 4 weeks	High score = high QoL	2 items	4-point scale, 1–4
Total			*28 items*	

* QLQ-MEL38 amended

with use, it will be even more relevant as a clinical tool. It will serve as valuable guide to a patient's need for referral for melanoma-specific concerns not previously identified in other questionnaires. The electronic capture and automatic generation of reports over time, to allow tracking of patient well-being, can provide a simple and effective means of improving patient-clinician communication and referral to other members of the healthcare team as needed.

26.2.2 Future Strategies for Measurement of QoL for Melanoma Patients

The era of more effective drug therapy has changed the face of QoL issues for melanoma patients. These drugs have their particular side effects, and survivorship issues that did not previously exist for melanoma patients will need to be addressed with the development of new QoL tools.

Routine collection of patients' QoL data in clinic settings has become a realistic prospect through a variety of media; for example, directly into the hospital's Information Technology systems in clinic or via smart devices by the patient at home. A pilot study is underway to embed electronic PROMS and patient-reported experience measures (PREMs) into routine care for patients with Stage III melanoma (ePROMs-MEL, https://www.anzctr.org.au/ACTRN12620001149954.aspx). A range of PROMs, including the MCQ-28 questionnaire, are being tested to track how melanoma patients are managing with their treatment over a 12-month period. This information will be useful as a means of highlighting which factors have a major, continuous impact and others which are shorter term and may vary at different time points. It is also hoped that it will improve clinical care, as patients who are having difficulty may be better identified and support services recommended in a timely fashion.

Accurate assessment of QoL impairment remains pivotal, and further research is required to establish a set of desired threshold scores which have the potential to screen patients and inform future decision-making by their treating care team (e.g. via the trial ePROMs-MEL) and to serve as an early warning of patients' unmet support needs. New clinical interventions may then focus on addressing these issues and the questionnaire would serve as a measurement tool to reveal the efficacy of these, following their implementation.

26.2.3 Utility-Based QoL in Melanoma: Instruments for Use in Economic Evaluation

Economic evaluations and cost-effectiveness studies of treatment in melanoma often require the health outcome to be reported in quality-adjusted life years (QALYs) [16] (see also Chap. 15, this volume). QALYs are a standard metric that combine length of life (survival time) with the quality of that life. The QoL is weighted in this calculation and when used in this way is called a 'utility'. Utilities are based on individual's preferences for difference health states – meaning a more desirable health state receives a higher weight. Health-related quality of life (HRQOL) utilities are measured on a 0 to 1 scale, where 0 indicates 'dead' and 1 indicates 'full or complete health'. It is possible that some people may rate their health status as 'worse than dead', and in this case, negative values are applied. Valuations of different health states on this scale are available from large population surveys in many countries [17–19].

26.2.3.1 Methods of Calculating Utility-Based Quality of Life

Utilities for economic evaluation can be generated through the use of standardised questionnaires called multi-attribute utility instruments (MAUIs) and their associated scoring manuals, or through direct elicitation methods such as the Standard Gamble or Time Trade Off. Utilities may also be generated by mapping the scores from other health-related quality of life questionnaires such as the QLQ-C30, to one of the above methods using a published algorithm [20]. Table 26.2 details utility-based QoL measures commonly used for assessing melanoma patients.

26.2.3.2 Choice of Utility Instrument

The choice of utility instrument will depend on the objectives (e.g. cost-effectiveness research [21] drug reimbursement, or to guide clinical care [22] or organisational benchmarking); the patient population being assessed (e.g. early-stage or advanced-stage melanoma); the treatments involved and their potential side effects (e.g. surgery, immunotherapy); and the resources available. Some measurements require a generic or cancer-specific utility instrument that has been validated in a melanoma population, whereas others require a melanoma-specific questionnaire that has scores that can be mapped so that utilities can be used.

The entire questionnaire should be viewed, to firstly assess the dimensions of QoL it covers, to assess if they are relevant to the stage of melanoma and the treatments being assessed. It is important to choose the instrument that will be sensitive to detecting both positive and negative changes in the disease or treatment [23]. Second, the health system context is important particularly if the country of health technology agency has a preference for one instrument or approach over another. For example, the EQ-5D is preferred in the United Kingdom and much of Europe [24]; the AQOL, EQ-5D, SF-6D, or HUI are preferred in Australia [16]. Third, there are pragmatic considerations to make in selecting which utility-based approach to use such as the length (number of items) of the questionnaire (i.e. brevity); availability of the instruments in representative languages; availability in digital formats for tablets/phones; and licencing fees.

26.3 QoL in Melanoma

26.3.1 Early-Stage Melanoma (Stage 0–II): Quality of Life and Unmet Needs

Despite a patient-centred approach placing an emphasis on patient needs, the QoL of early-stage (AJCC Stage 0–II) melanoma patients is often overlooked [25], likely due to the good prognosis and less invasive treatments associated with the early stages of melanoma compared to other cancers [26]. As a result, patients who may require assistance are seldom identified and their needs are not addressed in a timely manner, often resulting in greater QoL impairment [27]. This is rarely the result of one variable: it is a combination of numerous patient factors and unmet needs

Table 26.2 Summary of utility-based methods for use in health economic evaluations commonly used in melanoma care

Name of approach	Developed by	Population weights (tariffs)	Time to complete	Dimensions covered	Number of questions or items	Where it can be sourced (websites)
Assessment of quality of life (AQOL) version 4D, 6D, 8D	Monash University, Australia	Australia	8–10 minutes, dependent on version	4–8 including independent living, happiness, mental health, coping, relationships, self-worth, pain, senses; dependent on version	12–35, dependent on version	www.aqol.com.au
EQ-5D	EuroQol	UK, USA, most European countries, Australia, New Zealand	3 mins	5 (mobility, self-care, usual activities, pain/discomfort, anxiety/depression)	5 – each with 3 or 5 levels and a visual analogue scale	www.euroqol.org
SF-6D	University of Sheffield, UK	UK	5 mins	12 (need to complete the SF-12 questionnaire)	12	www.qualitymetric.com; www.shef.ac.uk/scharr/sections/heds/mvh/sf-6d
Health utilities Index (HUI)	Health utilities index, Inc	Canada, UK	8–10	9 (vision, hearing, speech, ambulation/mobility, pain, dexterity, self-care, emotion, cognition)	15	www.healthutilities.com

across varying categories, often compounded by the actual or perceived outcomes of treatment. This subsection outlines patient factors that relate to the association between common treatments and QoL, and the frequently reported unmet needs of early-stage melanoma patients.

26.3.1.1 Wide Local Excision and Scaring

Available evidence suggests that a negative self-perception of scaring and body image after melanoma skin excision is strongly associated with decreased QoL [28], more so than illness-related variables or demographics [29]. This altered body image is likely due to the appearance of the scar not matching the patients' expected appearance pre-surgery [30]. The scar is often perceived as worse than what the patient expected, affecting the patients' confidence in their appearance as they become self-conscious of the scar [30, 31]. As a result, these patients may experience distress, anxiety, or depression, impacting their QoL.

Women are more likely to report a negative body image. Sixty-four per cent of female patients rated their appearance as worse post-treatment in a North American survey, with 23% also unsatisfied with the appearance of the surgical site [32]. Furthermore, 10% of these female patients presented with symptomology indicating depression. Similar results were reported in Italy [29], the United Kingdom [33], and the United States [34].

The size of the excision is also a contributing factor to negative self-perception. Patients who received a 3-cm excision experienced significantly poorer physical and mental functioning compared to those who received a 1-cm excision [33], with excision on distal extremities also resulting in decreased QoL compared to proximal extremities [32]. Despite this, overall QoL improved with time since excision [32–34].

Therefore, it can be surmised that the perception of the scar itself is a primary factor influencing patient QoL, often leading to distress or adjustment [29]. In particular, healthcare professionals should aim to provide patients with a more 'realistic' expectation of their scar appearance pre-surgery, mitigating the decrease in patient confidence and self-image post-surgery [28, 30].

26.3.1.2 Sentinel Lymph Node Biopsy (SLNB)

SLNB is an important surgical procedure to provide prognostic information for early-stage melanoma patients, but it can result in mild lymphoedema. Despite its utility, many patients who undergo SLNB have no evidence of disease in the sentinel node, and thus undertake this procedure for prognostic information, rather than therapeutic intervention [35]. This can have a substantial impact on patient QoL, as complications may occur in 11% of SLNBs [36].

Despite the complication rate, 89% of Australian patients indicated that they would electively undergo an SLNB again [37]. Furthermore, no association between patient response and surgical complications or lymphoedema was evident in analysis, demonstrating that SLNB is well accepted by patients. The acceptance of SLNB is likely due to the increased sense of security provided by the procedure, as 96% of patients stated the period after surgery was less stressful due to the prognostic information provided by the SLNB [37]. However, it should be noted that pain as a result of SLNB remains a predictor of negative QoL outcomes [38].

Time since surgery is an important factor predicting the QoL of patients who undergo SLNB. Patients in multiple studies followed-up within 3 months of surgery had decreased physical and functional well-being resulting from their SLNB [39–41]. However, their QoL improved with time for 2 years post-surgery. Interestingly, several studies even found patients post-SLNB reported a significantly higher QoL compared to the population norm [39, 40, 42]. This evidence suggests that the detrimental impact of SLNB on patient QoL and well-being is only temporary, often returning to normal levels over time.

QoL likely returns to normal over time in part due to a *response shift* in patients.

Response shift is a change in a patient's self-evaluation due to changes in their internal standards, values, or definitions of a concept or construct [43]. These changes are often due to a significant change in the status quo of a patient's health, such as receiving a diagnosis of, or completing treatment for, melanoma. Thus, melanoma survivors may reassess their self-evaluation or life values, adopting a more positive outlook, meaning melanoma patients will likely understand and interpret questions and responses in QoL assessments differently to the general population [44, 45]. This may influence the results of analyses where self-report is required [43] which may need to be taken into consideration when comparing melanoma patients and the general population.

26.3.1.3 Lymphoedema

SLNB can lead to the development of lymphoedema, which results in a significantly worse overall QoL [44, 46]. Patients with lymphoedema also experience significantly worse body image, role functioning, and social functioning [44]. Lymphoedema likely affects these aspects of physical well-being through tiredness, discomfort, fatigue, and pain in the effected limb [44, 46].

With regard to body image specifically, women were significantly more likely to report a negative body image related to their lymphoedema [44, 46]. This may be due to the wearing of compression garments or visible changes to skin, which can be distressing to female patients as previously discussed [44]. Australian evidence further suggests that the perception of limb size is significantly associated with patient QoL, more so than the objective size of the affected limb [46].

26.3.1.4 Early-Stage Melanoma and Unmet Needs

Up to 55% of early-stage melanoma patients report an unmet need [26, 47, 48]. A systematic review [49] and evidence from the United Kingdom [30], the United States [50], Germany [51], and Australia [52] confirm that information needs are the most common category of unmet needs reported by melanoma patients. A unique feature of melanoma patient self-care is the need for self-monitoring skin checks to detect recurrence earlier and detect new primary melanomas and the use of sun protection. A detailed analysis of the most commonly reported informational unmet needs in an Australian study reflects this and showed the majority involved topics important to the patient, such as [52]:

- Side effects of long-term sunscreen use
- The differences between normal and dysplastic moles
- The role of genetic factors in melanoma diagnosis and recurrence
- The risk of children or grandchildren developing melanoma
- New advances in treatment
- Prognostic information

Patients further expressed that they wanted this information in easy-to-understand language, suggesting a notable proportion of patients may experience difficulty understanding the information provided to them. A further practical suggestion was the need for a folder, or some other simplifying tool, that contained all their melanoma-related documents [52].

Communication and emotional support from their healthcare professional was also highlighted as a significant unmet need [51, 53], with patients reporting their doctor seldom asked how they were coping with their diagnosis and treatment. A systematic review provides further evidence that many patients desire more emotional support from their clinician throughout survivorship [54].

Predicting unmet needs is inherently complex due to the myriad of contributing factors at the patient, provider, and system levels. There is some evidence that suggests unmet needs are most commonly associated with the psychological and emotional aspects of living with cancer, followed closely by the physical aspects and lifestyle changes associated with a diagnosis of melanoma [26, 53]. Patients who are divorced, separated, or widowed are significantly more

likely to have at least one unmet need [55]. Interestingly, cohabitating with a partner can directly influence patient quality of life in both a positive and negative manner, warranting further investigation on this topic [56]. Younger patients are also significantly more likely to report an unmet need, specifically relating to their psychological well-being [55]. Patients tend to experience most intense unmet needs up to 3 months post-diagnosis, but some patients continue to report significant issues, particularly related to disease recurrence and prognosis [50, 55].

Despite the lack of empirical evidence and complexity of screening for, and acting upon, patient-reported unmet needs, best practice is providing care with a patient-centred approach [55]. Further investigation is needed regarding the unmet needs of early-stage melanoma patients, particularly around timely identification and assessment of unmet needs, as well as exploration of effective avenues for support, that are both acceptable to the patients and clinicians.

26.3.2 Late-Stage Melanoma (Stage III–IV): Quality of Life and Unmet Needs

26.3.2.1 Stage III Disease: Quality of Life

Patients with Stage III melanoma experience multiple challenges related to their QoL. The literature has focussed predominantly on the impact of diagnostic and therapeutic procedures on QoL. However, there are few studies examining the broader psychosocial experience of this patient group, with many studies including patients with Stage I-III disease despite substantial differences in their staging, treatment, and prognosis. The impact of diagnostic investigations (imaging and SLNB), therapeutic procedures (lymph node dissection [LND], isolated limb infusion [ILI], and isolated limb perfusion [ILP]), and adjuvant and neoadjuvant drug therapies on QoL is reviewed here.

Imaging The impact of radiological staging with computed tomography (CT) and positron emission tomography (PET) on patient burden and satisfaction was explored by Bastiannet and colleagues [57]. Patients reported that both modalities were well tolerated, with >50% experiencing no burden during PET and 65% experiencing no burden during CT. Given imaging is required for initial staging as well as surveillance following treatment for Stage III disease, it is pleasing to note overall low levels of patient burden from these investigations. Nevertheless, attention should be paid to explaining these procedures to patients to reduce discomfort or burden.

Sentinel Lymph Node Biopsy and Lymph Node Dissection Two studies compared the impact of SLNB and LND on QoL in patients with Stage III melanoma. A case-control study, examined whether LND resulted in more postoperative complications and inferior QoL outcomes compared to SLNB with Stage III melanoma [42]. Whilst the study confirmed that LND was associated with more postoperative complications (including lymphoedema) compared to SLNB alone, overall QoL was similar between the two groups. Similarly, Egger et al. also confirmed that LND was well-tolerated, with similar QoL outcomes post procedure compared to SLNB alone [58]. However, neither study specifically measured the incidence of lymphoedema nor the impact of lymphoedema directly on QoL.

Patients who develop lymphoedema post SLNB or LND may experience a negative impact on multiple domains of QoL, as described in the early-stage melanoma section above. In a review of qualitative studies of patients with Stage III melanoma with lymphoedema, Dunn et al. described the distress associated with their perceived disfigurement, the discomfort associated with wearing revealing clothes, and negative body image [30, 59, 60] . Patients would attempt to minimise this impact through cognitive reframing, or attempting to conceal lymphoedema with clothing or cosmetics [30]. Two single institution quantitative studies have also highlighted the impact of lymphoedema on QoL [44, 61]. Upper or lower limb lymphoedema was associated with inferior QoL scores and increased interference

with activities of daily living, with one study also reporting inferior QoL in role and social functioning domains and financial difficulties [44].

Therefore, whilst LND may result in more postoperative complications than SLNB, the procedure in and of itself may not result in inferior overall QoL. However, if patients develop lymphoedema, this can have a negative impact on multiple QoL domains. The introduction of ultrasound surveillance rather than completion LND in patients with SLNB positive disease as a result of the findings of the MSLT-II [62] and DeCOG [63] studies, which showed no survival benefit with completion LND, will reduce the number of patients proceeding to a completion LND. Furthermore, trials of neoadjuvant systemic therapies, such as the PRADO expansion cohort of the phase 2 OPACIN-NEO study, are currently investigating whether patients with palpable nodal disease and a complete pathological response to neoadjuvant immunotherapy could avoid an LND [64].

Isolated Limb Infusion/Isolated Limb Perfusion ILI and ILP are used in the management of intransit melanoma metastases. Both procedures involve isolating the venous and arterial circulation of a limb with a tourniquet and then circulation of chemotherapy within the limb. Two prospective studies have examined the impact of ILP [65] and ILI [66] on QoL outcomes. In ILP, a transient reduction in FACT-G and FACT-M scores was noted at 3 months post procedure due to local toxicity [65]. This was not seen in the ILI study at 3 months, and fewer patients reported pain, numbness, or swelling in the affected limb compared to baseline [66]. However, at 12 months post procedure, patients undergoing ILP who had a complete response to treatment had similar QoL compared to baseline. Overall, ILP and ILI are well-tolerated procedures with minimal sustained impact on QoL.

Adjuvant Drug Therapy for Stage III Melanoma The introduction of adjuvant immunotherapy and targeted therapy for resectable Stage III melanoma has created new QoL challenges in this patient population. Adjuvant drug therapy is used postoperatively to reduce the risk of recurrence. All immune therapies in the adjuvant setting appear to maintain QoL throughout treatment [67–70], but longer-term follow-up is required to assess the impact of persistent immune related adverse events on QoL.

The BRIM8 [71] and COMBI-AD [72] studies included patients receiving adjuvant targeted therapies (vemurafenib and adjuvant dabrafenib and trametinib, respectively). The BRIM8 study reported a clinically meaningful decline in global health scores and QoL scores during cycle 1, which then improved but remained below baseline for the remainder of the treatment period, followed by a recovery to baseline scores post completion of adjuvant therapy. In contrast, the COMBI-AD study found no change in QoL over the course of treatment, despite the significant proportion of patients experiencing fatigue (7%), pyrexia (63%), or who discontinued treatment due to an adverse event (26%). The lack of significant impairment of QoL for these new adjuvant drugs may be real, but it may also be explained by the absence of a suitable PROM for measuring side effects associated with therapy, lack of data on the sensitivity of these measures to detect clinically meaningful deterioration in functioning, and differences in the timing of assessments. This highlights the importance of selecting appropriate PROMs for assessing symptomatic adverse events and QoL and careful timing of assessments to gain an accurate picture of the impact of therapies on QoL.

The novel use of drug therapy prior to surgery (neoadjuvant immunotherapy and targeted therapy) for resectable Stage III melanoma has been explored in several ongoing studies, and QoL outcomes are yet to be reported. However, the PRADO study has reported QoL outcomes for patients who undergo neoadjuvant immunotherapy, followed by either removal of only the index lymph node or therapeutic LND [64]. As expected, this demonstrated an improvement in surgical-related adverse events (all grade: 41% vs. 81%) as well as improved physical, role, social functioning, and melanoma surgery subscale scores for the index nodal procedure group.

This highlights the possible QoL benefits that may be achieved through improved pathological responses to neoadjuvant therapies.

Overall, more prospectively collected, longitudinal QoL data is required to further our understanding of the impact of investigations and treatment on QoL in patients with Stage III melanoma. Specific PROM strategies measuring adverse events and QoL, completed at carefully considered time points, will be helpful in accurately measuring the acute and chronic effects of treatment and determining the value of neoadjuvant versus adjuvant therapies. Novel trial designs, such as the PRADO study, with HRQOL improvements as an endpoint, will also help to develop treatment strategies that improve disease-related outcomes as well as QoL.

26.3.2.2 Stage IV Disease: Quality of Life

The QoL of patients with metastatic melanoma has significantly improved with the advent of effective systemic therapies.

Immunotherapy Multiple Phase 3 RCTs of pembrolizumab [73, 74], nivolumab [75], and combination ipilimumab and nivolumab [76] have demonstrated maintenance or improvement in QoL during treatment, despite adverse side effects [73–76]. The tolerability of these regimens has also been demonstrated in real-world data [77, 78].

However, data on the longer-term impact on QoL of receiving immunotherapy in patients with metastatic melanoma remains limited. A small study by Boedkhout et al. showed long-term survivors on ipilimumab scored significantly lower on physical, cognitive, role, and social functioning, as well as had higher symptom burden in terms of fatigue, dyspnoea, diarrhoea, and financial impact compared to controls [7]. This may contribute to the development of appropriate survivorship care for those patients on ipilimumab. Further work is needed to explore long-term QoL outcomes in patients receiving single-agent anti-PD1/PDL1 and combination immunotherapy.

Targeted Therapy Multiple Phase 3 RCTs have examined the combination of BRAF and MEK inhibitors and associated QoL implications. BRAF inhibitors alone show a poorer QoL compared to combination BRAF and MEK inhibitors [79–81]. Real-world data for patients receiving targeted therapy has highlighted a deterioration in QoL in comparison to immunotherapy. The acute and chronic toxicities associated with targeted therapy may therefore have an adverse effect on QoL. This is important to consider, given that these therapies need to be continued until disease progression.

26.3.2.3 Stage III and IV Disease: Unmet Needs and Survivorship Concerns

The survivorship concerns and unmet needs of patients with Stage III and Stage IV melanoma are evolving as treatment advances alter the prognosis of this patient population.

Stage III Melanoma: Unmet Needs and Survivorship In Stage III disease, few studies have focused specifically on patients' survivorship needs. Qualitative and quantitative studies have examined survivorship issues in patients with Stage I-III disease, with only small number of patients with Stage III disease. Therefore, findings suggestive of excellent QoL comparable to or sometimes better than the normal population may not be applicable to those with Stage III disease [30, 40, 55, 82]. A single qualitative study of patients with Stage IIIB-IV disease identified psychological concerns including worry, fear, and thoughts of death as common in this patient population [83]. Social impacts were also noted, including limitations on limitations on leisure activities and social functioning. A cross-sectional UK survey of 472 patients, including 28% of whom had Stage III disease, examined supportive care needs and anxiety and depression [55]. In patients with Stage III disease, higher levels of unmet supportive care needs were noted compared to patients with Stage I and II disease, as well as higher rates of self-reported anxiety and depression. Qualitative studies in Stage III patients regarding return to work show that

patients often felt unsupported by their colleagues/ managers and that there was a lack of understanding in the workplace regarding the impact of their cancer and recovery [59, 84].

The advent of adjuvant and neoadjuvant immunotherapy and targeted therapy will further improve the prognosis of patients with Stage III disease. Research is therefore urgently needed to understand the specific challenges and unmet needs in those with Stage III disease who receive these novel therapies. Inclusion of PROMs as part of ongoing trials, as well as in routine care, examining symptoms, psychological concerns, and social and functional issues such as return to work and financial stress will help to fill this knowledge gap.

Stage IV Melanoma: Unmet Needs and Survivorship The literature regarding survivorship and supportive care needs in patients with metastatic melanoma prior to the advent of immunotherapy and targeted therapy reflected the lack of effective treatment options and the subsequent rapid deterioration in all aspects of a patient's QoL [11, 59]. However, therapeutic advances have significantly improved the prognosis of many patients with metastatic melanoma, resulting in increasing supportive care and survivorship research in this population.

It is now recognised that there is an emerging population of patients with durable disease control following immunotherapy or targeted therapy. These patients experience a unique set of physical, psychological, social, and functional challenges and unmet needs. Chronic immunotherapy-related toxicities have been reported in several single-centre studies, including rashes, arthralgias, myalgias, fatigue, and insomnia [85, 86]. Chronic toxicities were also reported for patients receiving targeted therapy including dry/itchy skin, arthralgias, diarrhoea, and fatigue [85]. Qualitative studies have emphasised the substantial impact of fatigue on activities of daily living, capacity to work, and all aspects of QoL [84]. Long-term immune-related adverse events including rash, colitis, hypothyroidism, hepatitis, and hypophysitis were reported, including in those who had already ceased therapy [86, 87].

Despite these significant long-term side effects, a systematic review of studies examining factors important to patients and clinicians when making decisions regarding immunotherapy for Stage IV melanoma showed that overall survival remained the primary concern of both groups, with impaired QoL due to adverse events a second-order consideration. Patients were willing to tolerate severe (and potentially irreversible) toxicities for small survival benefits [88].

Psychological morbidity was common in this survivor group, including difficulties dealing with uncertainty, an inability to plan for the future, and a feeling of frustration, hopelessness, and loss of control [59, 84, 85]. Patients also reported anxiety awaiting test results, fear of their melanoma recurring or progressing, and death [85]. Many patients reported issues with anxiety and depression [86]. Patients expressed regret about past sun exposure, concerns about future sun exposure, and possible melanoma risk to the family [85]. Formal neurocognitive outcomes have also been examined in two small single-centre studies of patients who had received ipilimumab more than 2 years ago [89] or pembrolizumab more than 6 months ago [90] using PROMs, standardised computerised neurocognitive tests, and semi-structured interviews. Clinically relevant levels of anxiety, fatigue, and subjective and objective neurocognitive impairment were present several years after treatment cessation. This resulted in a lower QoL at all follow-up time points, including physical, cognitive, emotional, and social functioning compared to European normative data. This highlights the ongoing emotional distress, fatigue, and neurocognitive impacts that can follow treatment with immunotherapy and the ongoing impact on QoL.

The social, financial, and functional concerns of long-term metastatic melanoma survivors have also been examined. Patients on long-term immunotherapy and targeted therapy reported difficulties undertaking domestic tasks, recreational activities, and planning/taking holidays [84, 85].

Financial difficulties have also been reported, including difficulty paying for transport/parking or accommodation (particularly in those who need to travel from a rural to an urban area to access treatment) [84], or accessing insurance payouts [85].

Understanding the experience of long-term survivors of metastatic melanoma is essential to improving their care. These studies provide insights into the issues faced by this population which are not captured by standard QoL measures. These include chronic toxicities from immunotherapy and targeted therapy; psychological concerns relating to an uncertain future, ceasing treatment, and concerns about cancer progression; and the difficulty balancing treatment with returning to work. Patients may benefit from discussions regarding long-term toxicities and treatment duration, tailored psychological support to manage anxiety and fear of cancer recurrence, and a survivorship care plan [85]. Interventions, including tailored exercise programs, to address immunotherapy-induced fatigue are being evaluated [84, 91]. Patients also require clear, tailored, and well-timed information regarding their diagnosis, prognosis, and treatment. Prospective, longitudinal patient-reported outcome collection from diagnosis would allow QoL outcomes to be measured in parallel with key events a patient's treatment and follow-up, building a more complete picture of their survivorship experience.

26.4 Patient Factors Influencing Quality of Life

26.4.1 Sex

A diagnosis of melanoma has a disproportionate impact on the psychosocial health of females [32, 38]. In the Netherlands, females reported a significantly larger variation in the emotional impact of their melanoma diagnosis, illustrating that men experience a more moderate emotional impact [40].

Literature is inconsistent in relation to influence of sex on QoL, with some studies failing to find significant association [26] and others reporting that females tend to experience worse overall QoL and greater psychological and emotional distress resulting from their diagnosis [92]. This may in part be related to female patients experiencing greater discomfort in their body image post-diagnosis and treatment, as female QoL is significantly higher when the melanoma (or resulting surgical scar) is located on proximal rather than distal extremities, decreasing their visibility [29, 32, 93, 94].

Female patients are significantly more likely to seek out shade or apply sunscreen when in the sun, or avoid sunny places entirely, whilst worrying about the effects of the sun on others [40]. Considering that a diagnosis of melanoma may have greater emotional impact on the mental health of females, it is unsurprising they are more likely to adopt and advocate for behaviours that may prevent melanoma diagnosis, progression, or recurrence in the future. This is despite many patients reporting frustration with others due to a lack of appreciation regarding the seriousness of melanoma and sun protection, regardless of gender [31].

26.4.2 Age

Similar to sex, age is a strong predictor of patient QoL, with older patients often experiencing a worse overall QoL [39, 40, 51, 93]. The decreased QoL in older patients is specifically associated with decreased physical functioning and increased melanoma-related symptoms [94]. Despite this, older patients also report improved emotional and social functioning, positive body image and fewer worries about the future in comparison to younger patients [94]. Therefore, although increasing age results in a decrease of overall quality of life and physical well-being, it also leads to improvements in self-perception, mental health, and social health [39, 55, 95].

Melanoma is the most frequent cancer that affects the 15–30-year-old age group. Gaps in support and information needs are emphasised in

younger melanoma survivors (aged 15–29) in conjunction with lack of information about sexuality and intimacy [96–98].

26.4.3 Significant Medical Comorbidities

Although limited research exists exploring select comorbidities, the available evidence is clear that an increasing number of diagnosed comorbidities is associated with a decrease in the QoL of melanoma patients. Experiencing at least one comorbidity was associated with decreased QoL through their impact on patient well-being [40, 51, 93–95, 99]. More research is needed to explore these results, preferably using longitudinal designs, which can explore causative pathways for this relationship.

26.4.4 Coping Strategies

Coping can be defined as the attitudes, actions, and beliefs with an adaptive purpose employed by a person when faced with a threatening situation and acts to protect the emotional state of the individual and to allow for psychological adjustment [100]. Several useful strategies have been identified for coping with the diagnosis and treatment of melanoma including maintaining hope, facing reality, expression of emotions, and seeking support from others [100]. Individual coping mechanisms have been shown to be related to individual changes in QoL with a positive association between higher coping skills and higher QoL [101].

The ability of a patient to minimise the impact of melanoma in daily life is important and is associated with all constructs of the QoL [102]. In melanoma patients, Kasparian et al. found that active and problem-focussed coping strategies are indicative of better adjustment to their melanoma [103]. Furthermore, social support that patients receive from family, friend, and health professionals is predictive for QoL and well-being [104].

26.5 Specific Impacts on Patients

26.5.1 Fear of Cancer Recurrence

Compared to other cancers, patients diagnosed with melanoma are relatively younger, and this, combined with the relatively good prognosis of most melanoma patients, means that a greater proportion of patients will live for many years with the history of melanoma. Fear of cancer recurrence (FCR) is worry that melanoma can recur or progress. It is a rational and normal response to the real threat of cancer recurrence. However, when elevated it can affect social functioning and psychological well-being. FCR has been identified as an important symptom of distress reported by both early- [53, 105] and late-stage melanoma survivors, and elevated FCR has been found to be associated with lower QoL and impaired social and emotional functioning [106].

Not only are these fears prevalent in the early-stage melanoma population, but they do not decrease significantly over time [52], with 44% and 48% of Australian patients reporting fear of cancer recurrence at 3 and 5 years post-diagnosis, respectively [26]. Late-stage melanoma patients are mostly concerned about the uncertainty about the future, both in terms of durability of response and potential side effects [107].

Patients who are female or younger are more likely to report FCR compared to male or older patients [105]. As FCR increases, patient QoL decreases, due to these fears impacting the long-term psychological well-being of patients [108, 109], which can lead to increased depression, anxiety, and stress [23, 105].

26.5.2 Distress and Depression

In melanoma, psychological distress has been reported as the most common psychological concern amongst patients [6] (see also Chap. 20, this volume). Around 30% of patients reported psychological distress indicative of a need for clinical intervention, including anxiety and/or

depression [103]. Depression was reported to be present 2 years after the acute initial phase of the treatment [110]. The presence of psychological distress is mostly explained by the uncertainty surrounding a cancer diagnosis [111, 112]. Distress and depression will impact significantly on the social and professional aspects of patients' lives. Furthermore, the presence of depression is associated with reduced functional status, lower treatment compliance, and prolonged hospitalisations [113, 114]. Depression affects the intensity of physical symptoms, but also complicates symptom management.

26.5.3 Pain

Pain is one of the most important determinants of QoL. For a melanoma patient undergoing surgery, the level of pain depends on the type of surgery. SLNB is rarely followed by long-term pain, while persistent pain and sensory symptoms appear to be common in patients undergoing LND [115]. Pain, especially joint pain, is also a common side effect for melanoma treatment including radiotherapy, targeted therapy, and immunotherapy [116].

26.5.4 Cost: Financial/Work/Time

Financial and time burden experienced by melanoma patients are strong predictor of patients' QoL. Melanoma diagnosis, treatment, and follow-up incur costs, toxicities, and time that limit participation in life activities, either directly through toxicities or indirectly through mechanisms such as stress, financial toxicity, fatigue, or lymphoedema [117, 118]. In particular, melanoma-related lymphoedema can interfere with activities of daily living [61] and has been found to be related to increased financial difficulties in patients [44]. Indeed, lymphoedema directly impacts work performance, time off work for its treatment, or maintenance of the current or future occupation [119].

Few studies are available relating to the important issue of cost for both early- and late-stage melanoma patients.

26.6 Impact of Melanoma on Partners, Families, and Social Supports

There is a paucity of literature regarding the impact of melanoma on carers and families. However, one small study showed that priorities of patients and carers for patients' QoL was different, with family being the number one priority over all stages of disease for patients and capability being the priority for carers [120].

The experience of carers of patients with metastatic melanoma has also been examined in a single-centre qualitative study [84]. Carers felt responsible for the correct identification and reporting of treatment-related side effects, including after treatment cessation. This highlighted the burden associated with managing symptoms and providing emotional support which can result in greater distress than other caregiving tasks. Specific training and support for carers is therefore needed for this patient group.

26.7 Melanoma Survivorship Compared to Other Cancer Patients

Survivorship issues are unique to each type of cancer, and melanoma, in particular, has its own set of issues and challenges. At the initial phase of diagnosis, issues of QoL and survivorship are generally related to physical well-being, side effects of treatment, and the psychosocial effects related to initial cancer diagnosis. However in the long term, described loosely as after treatment cessation, physical issues are less prevalent, and addressing psychosocial factors may play a larger role in patient well-being [26, 121, 122]. These physical symptoms are largely non-specific including pain, insomnia, fatigue, dyspnoea, cognitive dysfunction, and gastrointestinal symptoms such as diarrhoea and nausea. Across both of these time frames, recurrence of cancer remains an important facet of melanoma survivorship which requires continual monitoring.

In patients diagnosed with melanoma, there is a general decline in QoL scores across all domains in the short term [94]. These measures are also significantly decreased when compared to the general population; however, they are higher when compared to other cancers, such as breast cancer [122, 123].

Melanoma patients tend to report behavioural changes following their diagnosis. However, information available related to behavioural modifications remains relatively limited. A recent review of post-treatment health behaviours among long-term melanoma survivors revealed that they frequently adopted diet, exercise, and life style changes after their diagnosis [124]. For melanoma patients, behavioural modifications related to sun exposure and also skin self-examination are crucial to help prevent future skin cancers and identify recurrence earlier and to optimise health status especially in the presence of other comorbidities. A single report demonstrated that the diagnosis of melanoma was positively associated with modified sun-related attitudes and behaviours, such as staying out of the sun and using protective measures, like sunscreen [125]. However, survivorship often extends beyond the person diagnosed and can affect family and friends, creating a 'teachable' moment for these other stakeholders. This may provide them with motivation to adopt their own skin cancer prevention techniques [126].

26.8 Interventions to Improve Quality of Life for Melanoma Patients

Given the significant distress and QoL impairments, patients diagnosed with cancer often report several clinical practice guidelines and advocate for timely identification and provision of supportive care interventions as a part of holistic cancer care [127]. A meta-analysis of psychosocial interventions in oncology, indicating small to medium effects on the QoL of patients and survivors, supports this recommendation [128]. However, the interventions included in this meta-analysis were predominantly implemented in female patients diagnosed with breast cancer, with the degree of relevance and transferability to melanoma patients unclear.

Disease-specific supportive care interventions are recommended [129]. Given that appropriate information is the most frequently reported unmet need reported by melanoma patients [49], it is imperative that the educational aspects of any QoL intervention include melanoma-specific information. Additionally, patients expect the intervention providers to have adequate melanoma-specific knowledge [130]. Furthermore, societal views may trivialise QoL difficulties that melanoma patients experience [110]. Primary melanoma patients tend to look relatively healthy, leading to a perception that the disease does not have significant consequences for their health. The fact that melanoma is rarely referred to as 'cancer' may further contribute to this separation between melanoma and cancer patients [110]. Therefore, it is not surprising that melanoma patients have reported difficulties in accessing generic oncological supports [131]. They also tend to decline generic interventions, as evidenced in the often-difficult recruitment of melanoma patients [132–135]. In contrast, melanoma-specific interventions have demonstrated excellent uptake and adherence [52]. Therefore, the following section will summarise the literature on the melanoma-specific interventions targeting different QoL aspects of patients and survivors. While the aim is not to present an exhaustive review of the literature, it is hoped it will provide clinicians and researchers an overview of research evidence for a range of interventions addressing different QoL aspects in this population.

26.8.1 Distress

Despite recommendations for routine distress screening and intervention in patients experiencing elevated distress levels [136], only two studies specifically addressed distress in melanoma patients [137, 138]. Both interventions were based on principles of cognitive-behavioural therapy and were offered to Stage I-III patients

who reported elevated distress levels. Bares et al. [137] provided a workbook and three individual sessions, while, Trask and Paterson [138] provided four manualised individual sessions. The contents of both interventions included relaxation training, challenging unhelpful thoughts, teaching problem-solving skills, and strategies for maintaining progress. Bares and Trask [137] demonstrated significant intervention effects on distress that were maintained at 5-month follow-up, in contrast to Trask and Paterson [138]. The intervention implemented by Trask et al. decreased patient anxiety, with this effect maintained at 6-month follow-up. Furthermore, intervention effects on other QoL variables (general health, vitality, social functioning, and mental health scores) that were apparent immediately post-intervention were not maintained during 2- and 6-month follow-up [138]. Bares and Trask [137] demonstrated economic benefit for their intervention, with the cost being offset by a reduction in distress-related telephone calls to physicians and nurses.

26.8.2 Fatigue

Despite fatigue being commonly reported by melanoma patients, melanoma-specific fatigue interventions are sparse, with only one pilot-study protocol identified, which detailed an exercise-physiology intervention – iMove [91]. According to this study protocol, it aims to recruit Stage IV melanoma patients on immunotherapy (see also Chap. 17, this volume). The intervention will be delivered over a 12-week period and will consist of an individualised exercise programme. This pilot study will aim to assess the intervention's feasibility and impact on fatigue and quality of life.

26.8.3 Fear of Cancer Recurrence

Two interventions were found to be effective in reducing fear of cancer recurrence in melanoma patients [52, 139]. These interventions target different melanoma patient groups, deliver different interventions, and utilise different modes of delivery. Although they both have data on the efficacy of their respective interventions in reducing fear of cancer recurrence post-treatment, only Dieng et al. present 12-month follow-up data [140].

The Melanoma Care Program was developed to support Stage 0-II melanoma patients at high risk of another melanoma [52]. This intervention included the provision of a booklet and three individual psychotherapy sessions delivered by a trained psychologist via telehealth [141]. Psychotherapy sessions were patient-centred and focused on providing empathic listening and understanding of patients' experiences, whilst supporting the development of helpful personal and interpersonal coping strategies. Both the educational booklet and psychotherapy sessions were well received by melanoma patients, as evidenced by patients' direct feedback, and excellent retention and adherence rates [142, 143]. In comparison to the control group, melanoma patients who received this intervention reported lower FCR, stress, and higher melanoma-related knowledge at 6-months follow-up [52]. While this intervention effect has reduced at 12-month follow-up, a significant difference for FCR was maintained between the intervention and control groups [140]. With the mean cost to deliver this intervention being AU$1614 per participant, this intervention was considered to be good value for money [144].

In contrast, Russell and Ugalde [139] developed an online mindfulness-based intervention to support Stage II and III melanoma patients with their FCR. This intervention consisted of a 6-week course, hosted online, and aimed to increase knowledge of mindfulness and support patients in developing daily practice. E-mail reminders were included to facilitate habit development. This intervention was designed to be self-managed, without the need for professional support. It was found to be feasible and acceptable by the patients, with preliminary evidence of the effectiveness of this intervention in reducing severity of FCR. However, when patients were experiencing clinically significant levels of FCR at baseline, this intervention seldom resulted in reduction of FCR below clinical levels [139].

Evidence of long-term intervention effects is not available at present, as well as information about the adequate intervention 'dose', as varied frequency of mindfulness practice was reported by the participants.

26.8.4 Social Support and Coping

Perhaps the earliest example of a structured melanoma-specific intervention was developed by Fawzy and Cousins [145]. A psychiatrist delivered the intervention through six weekly sessions to Stage I and II melanoma patients following surgery. The intervention consisted of education about melanoma and health behaviours, stress management, enhancement of coping and problem-solving skills, and social support from both the facilitators and group members. At 6-month follow-up, intervention resulted in significantly higher vigour, better coping styles and lower depression, fatigue, confusion, and mood disturbance [145]. Additionally, patients in the intervention group experienced positive immunological changes at 6-month follow-up [146]. At 5-year follow-up, patients that received this intervention had better survival rates and a lower melanoma recurrence rate [147]. At 10-year follow-up, while the survival benefit has reduced, melanoma patients who participated in the intervention still maintained a threefold reduction in the risk of death, when compared to controls [148].

Boesen and colleagues [149] adapted this intervention into a multi-disciplinary format, while still using the original manual [145]. The intervention consisted of six group sessions, which were slightly longer in duration (2.5 hours in contrast to 1.5 hours) and delivered by physicians (melanoma information), nurses (sun exposure and preventative behaviours), and a psychologist (stress management and coping). At 6-month follow-up, the intervention group reported a significant reduction in fatigue and mood disturbance, increased vigour, and better coping mechanisms. Intervention effects were not maintained at 12-month follow-up [149]. Unfortunately, the survival benefit reported by Fawzy et al. [148] was not replicated [150].

This intervention was also adapted by Fawzy [151] to the individual format, delivered by a nurse. An educational manual, collating the information from the original intervention, was provided to Stage I and II melanoma patients. Patients randomised to the intervention group reported significant reductions in distress, anxiety, fatigue, confusion, somatisation, and unhelpful coping strategies and improvement in vigour at 3-month follow-up. Although this demonstrated the effectiveness of this individual, nurse-delivered intervention, some patients have reported that they would benefit from the group dynamics – feeling validated and supported by other melanoma patients. Furthermore, group format was also judged to take up less therapist time per patient than individual [151].

Pedersen and Schmidt [152] reported the preliminary outcomes of an unstructured support group, which was created and led by patients, with a medical practitioner regularly attending to answer questions that the group had about melanoma and treatment. Advanced melanoma patients who were starting their treatment were encouraged to participate in this group to access social support from patients in similar situation. Qualitative interviews about the perceptions of the group revealed benefits including changed attitude to hospital processes, increased knowledge and confidence in asking questions of healthcare professionals, and increased self-efficacy and coping. A number of participants commented that the feelings of shared fate, identification, and bond through common experiences were in contrast to frequent perceptions of isolation from their healthy friends and family.

26.8.5 Service Models

With supportive care interventions demonstrating positive outcomes on melanoma patients' quality of life, research on translating interventions into clinical practice and innovative service models are beginning to emerge. Studies have focused on developing processes for timely identification and referral of melanoma patients who may benefit from additional support [153–157], as well as

implementing evidence-based practice into clinical care [158].

The crucial first step in supportive care is the assessment of melanoma patients' functioning and unmet needs, which will allow for timely identification of patients that may require additional support. To achieve this goal, patient navigators [153, 154], nurses [155], social workers [156], and supportive care physicians [157] have assessed melanoma patients' unmet needs and provided individualised support plans that generally included information (melanoma-specific medical information, preventative behaviours, coping, decisional support) and service coordination (e.g. referrals to support groups, legal support, exercise physiologist, nutritionist/dietitian, psychologist, complimentary therapies). Most service models included a well-accepted and validated patient-reported outcome measures to support needs identification [153–155], while others used clinical interviews [156, 157]. Preliminary evidence suggests that these interventions are feasible to implement in clinical practice [157] and are acceptable to the patients [154–156] and clinicians [154]. The PROMs were perceived as easy to complete, and seen as a conversation starter about the issues that would not have ordinarily been discussed in clinics [155]. The interventions recommended were generally implemented by the patients [154]. Preliminary data on the effectiveness of these service models indicates that they may result in increased self-efficacy [153], with the effects on distress, QoL, and satisfaction with oncology services inconsistent, with some studies reporting no effects on these outcomes [153, 154], while others small but significant improvements [156].

Lynch and Katona [158] reported preliminary findings about Fear-Less programme, which is the first melanoma-specific translation of evidence-based practice into routine clinical practice. Using a stepped-care approach, well-accepted and validated measures of FCR/progression were used to identify Stage IV melanoma patients who were experiencing significant distress and offer them varying intensity of intervention, depending on the severity of their symptoms. Individuals reporting clinical FCR/progression were offered individual therapy according to the adapted Conquer Fear [133] intervention. The pilot results indicate that this intervention is feasible and acceptable to the patients and provides preliminary support for the effectiveness in reducing FCR.

26.9 Impact of Quality of Life on Survival

There appears to be contradictory views on the impact of psychosocial factors, including baseline personality, coping style, psychological interventions, and global QoL, on development of, relapse and survival in all cancers (see also Chap. 14, this volume). A review of the literature however suggests that there is a positive relationship between QoL and survival [159, 160]. There is also a suggestion that psychoneuroimmunology (stress, coping patterns, and emotional adaptation) and its link to progression of cancer may be more important in melanoma, as it is a more immune-related tumour [161].

An increased risk of developing melanoma may be related to a history of depression [162], and even in early-stage melanoma, a view that treatment was curative [163] and improved psychosocial health with interventions [148] appeared to improve survival. Improved survival for metastatic melanoma patients was related to higher global QoL scores [164] and again, if they viewed their treatment as curative [165].

26.10 Conclusion

With the advancement of medical treatment resulting in melanoma patients living longer, there is an increased focus on QoL issues. We are only beginning to understand the impact of melanoma diagnosis and treatment on QoL of patients, the determinants of good/poor QoL and how to measure and support QoL. There is a handful of well-designed studies investigating these aspects of QoL, with majority of research in preliminary stages. Current literature leaves several important questions yet unanswered: How do we best measure QoL? What constitutes 'good'/'poor' QoL?

How do we best identify melanoma patients with unmet needs? Who is best placed to identify those in need of additional support? What are the active ingredients that most contribute to the effectiveness of QoL interventions? What is the most efficacious dose for interventions? Do booster sessions help sustain the intervention effects, as they invariably reduce over time? What intervention delivery mode (e.g. individual, structured/unstructured groups, face to face, telephone, online) is most effective and sustainable, given limited resources? It is hoped that future research answering these questions will contribute to improvement in QoL outcomes by making the evidence-based interventions available to melanoma patients that need them.

26.11 Questions That Can Be Used for Learning/Testing

1. Which QoL issues appear to be an issue in melanoma patients?
2. What melanoma-specific QoL assessment tools are available?
3. What components of interventions seem to be helpful in addressing QoL issues?

26.12 A Topic for Discussion That Can Be Used for Teaching

A patient recently diagnosed with melanoma presents to your clinic and reports difficulties in some aspects of QoL. What steps would you follow in assessment and support of this patient? Who would be the most suitable professionals that may help this patient that are in your local area?

26.13 Further Reading List

The following list presents literature that extends the contents of this chapter. Readers looking for in-depth information and further material are advised to consult the following sources.

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Melanoma Institute Australia. Melanoma treatment; resources for patients and clinicians. https://www.melanomaeducation.org.au

26.14 Research in Context

The databases of PubMed and Medline were searched for English journal articles between 2015 and 2020 using the search terms ‘melanoma’, ‘quality of life’, ‘supportive care’, ‘quality of care’, and ‘survivorship’. Where possible, meta-analyses and randomised trial data were included; however, given the nature of this chapter, there was little evidence-based data available.

This chapter summarises the current QoL and survivorship issues for melanoma patients, which is rapidly changing given the new paradigm of more effective drug therapy for melanoma.

It is evident that there is much scope for further research related to QoL assessment and interventions for melanoma patients, to provide evidence for improved practice.

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Index

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